"STUDY OF PHYSICAL, SOCIAL AND COGNITIVE FUNCTIONING OF CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA"

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INSTITUTE OF CHILD HEALTH AND

HOSPITAL FOR CHILDREN

MADRAS MEDICAL COLLEGE

CHENNAI

CERTIFICATE

This is to certify that dissertation entitled **"STUDY OF PHYSICAL, SOCIAL AND COGNITIVE FUNCTIONING OF CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA"** submitted by **Dr. C. REKHA** to the faculty of paediatrics, The Tamilnadu Dr. M.G.R. Medical University , Chennai in partial fulfilment of the requirement for the award of M.D. Degree in Paediatrics is a bonafide research work carried out by her under direct supervision and guidance.

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Chennai-600008.

CERTIFICATE OF THE GUIDE

This is to certify that the dissertation entitled "**STUDY OF PHYSICAL, SOCIAL AND COGNITIVE FUNCTIONING OF CHILDREN WITH CAH**" submitted by **DR. C. REKHA,** in partial fulfillment for the award of the degree of Doctor of Medicine in Pediatrics by The Tamilnadu Dr. M. G. R. Medical University, Chennai is a record of original work done by her under my guidance and supervision in the Institute of Child Health and Hospital for Children, Madras Medical College during the academic year 2013-16.

Place: Chennai

Date:

PROF.DR.S.SUNDARI,M.D.,DCH,

Director and Superintendent,

Unit chief & Research Guide,

Institute of child health and hospital for Children,

Chennai-600008.

DECLARATION

I **Dr. C. Rekha** solemnly declare that this dissertation entitled **"STUDY OF PHYSICAL, SOCIAL AND COGNITIVE FUNCTIONING OF CHILDREN WITH CONGENITAL ADRENAL HYPERPLASIA"** was done by me at Institute of child health, Madras Medical College under the guidance and supervision of **Prof.Dr. S.Sundari, M.D.,DCH..** This dissertation is submitted to the Tamilnadu Dr . M.G.R. Medical University , Chennai in partial fulfilment of the rules and regulations for the M.D degree examination in paediatrics.

DATE : Signature of candidate

PLACE : Chennai **(DR. C. REKHA)**

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Introduction:

Definition:

Congenital Adrenal Hyperplasia(CAH) is defined as a genetic problem involving steroidogenesis in adrenal gland due to enzyme deficiencies, most common being 21 hydroxylase deficiency[1]. This would lead to hypercortisol deficiency and accumulation of intermediate metabolites, thereby stimulating pituitary gland to produce more ACTH (Adreno Cortico Trophic Hormone). ACTH stimulates adrenal gland resulting in hyperplasia. The accumulated metabolites are the cause for symptoms in CAH, in addition to steroid deficiency.

Adrenal Glands:

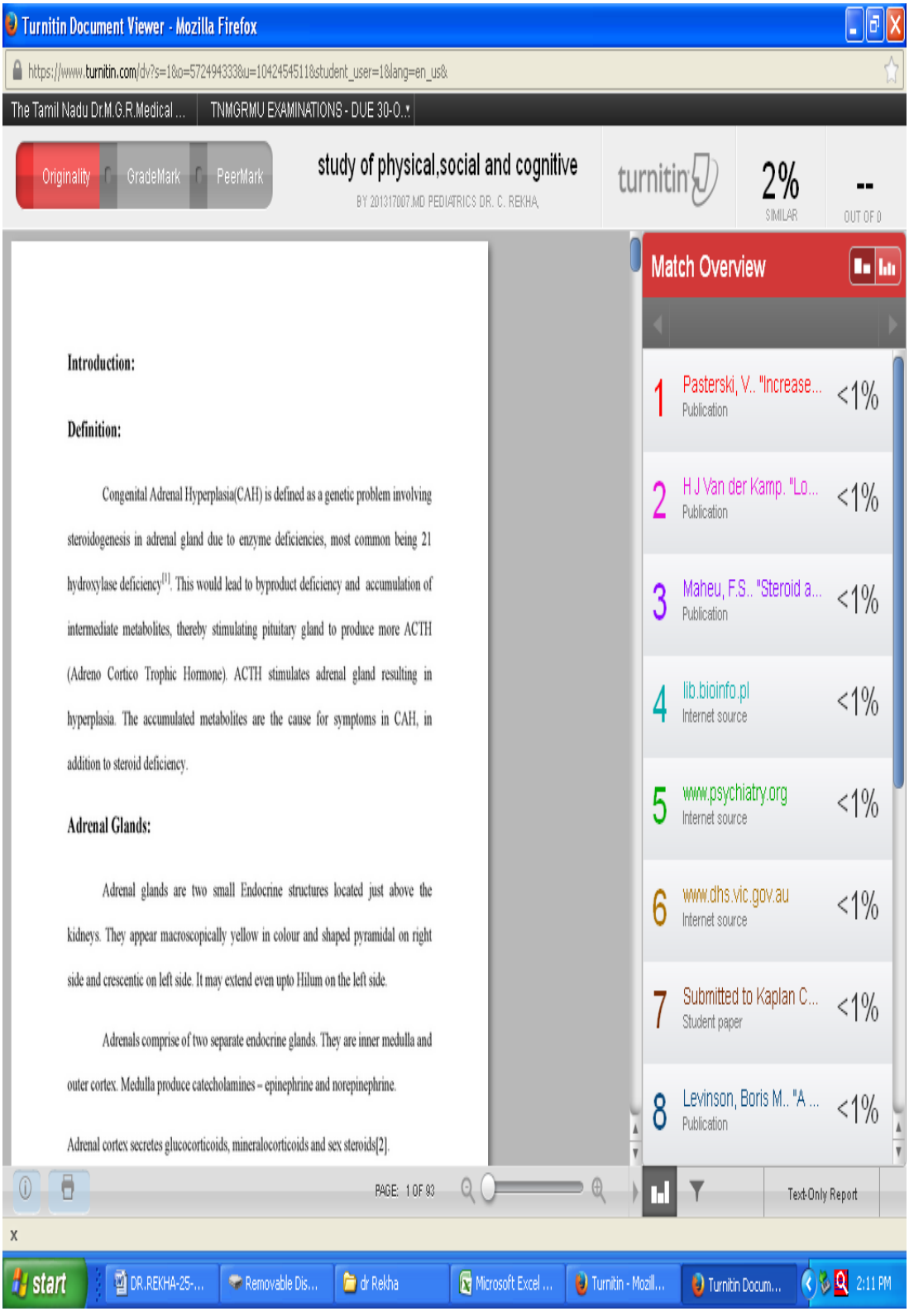
Adrenal glands are two small Endocrine structures located just above the kidneys. They appear macroscopically yellow in colour and shaped pyramidal on right side and crescentic on left side. It may extend even upto Ilium on the left side.

Adrenals comprises of two separate endocrine glands. They are inner medulla and outer cortex. Medulla produce catecholamines – epinephrine and norepinephrine.

Adrenal cortex secretes glucocorticoids, mineralocorticoids and sex steroids[2].

Adrenal medulla is essential for emergencies while adrenal cortex is essential for life.

1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CONTENTS

Study of physical, social and cognitive functioning of children with congenital adrenal hyperplasia

Abstract:

Aim and objective: To study the physical, social and cognitive functioning of children with congenital adrenal hyperplasia.

Methodology: All clinically and biochemically confirmed cases of CAH on treatment were included in the study based on the inclusion and exclusion criteria. Totally 55 cases were enrolled.Detailed history is obtained from patient's records. Clinical examination done and anthropometric measurements were plotted on standard charts. Investigations like 17OHP levels and x-ray for bone age were done for all. Vineland social adaptive behavior scale and CBCL were used for determination of social functioning. Cognitive assessment was done using different scales appropriately used for different age groups.

Results: About 62% were salt wasters and 38% were simple virilisers. 86% of these kids were born of consanguineous marriage. 16% had statistically significant family history when analysed comparing the two types of disease. 20% of these kids had altered growth pattern with 9% of them with short stature and 11% of them with their height >+3 z scores. Steroid dose and Height showed poor negative correlation with p value of 0.007. 20% of our kids were obese. None were hypertensive. But 22% of them were in the prehypertensive state. 4% of them had advanced bone age. 40% of kids had moderately low social adaptive skills. 20% of our population were aggressive. 15% of them had ADHD. 53% of them had only borderline IQ levels.

Conclusion: CAH is a disease which not only affects growth but also may reduce the cognitive functioning in children. It also increases the risk for psychiatric disorders**.** Hence it is necessary do psychological and cognitive assessment in CAH children.

Key words: congenital adrenal hyperplasia, steroids, height, aggression. hyperandrogenism, IQ.

INTRODUCTION

Definition:

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Embryology

Adrenal medulla is a derivative of neuroectoderm whereas Adrenal cortex is from mesoderm. Three zones under adrenal cortex are:

- Zona Glomerulosa
- Zona Fasciculata
- Zona Reticularis

From outer to inner zone, hormones produced are Aldosterone, Cortisol and Androgens respectively. Even at the early period of gestation, normal feedback relationships are maintained. Two important genes involved in adrenal gland development are

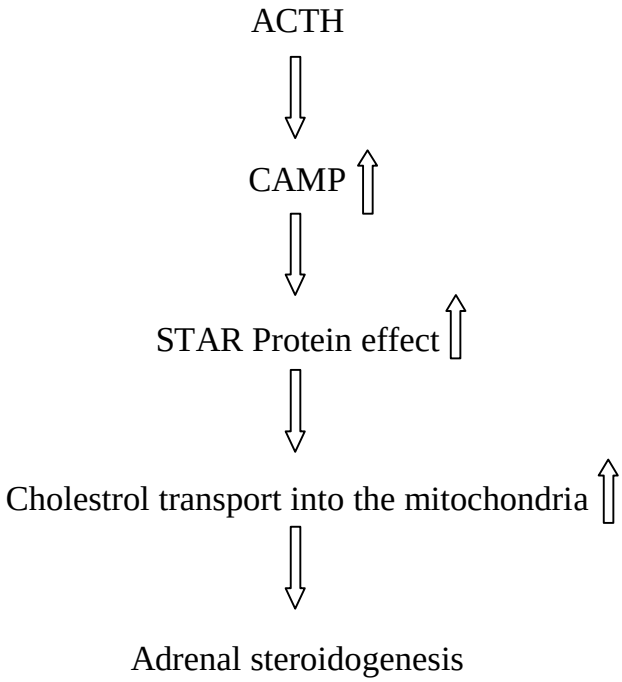
- SF1
- DAX1

Development of Adrenals:

Gestational age	Development
3-4 weeks	Primordium of Adrenals appear
5-6 weeks	Gonadal ridge produce steroidogenic cells of adrenals
6-8 weeks	Gland enlarges rapidly and sympathetic neural cells enters in
7-10 weeks	Active steroidogenesis starts[3]
20 weeks	Adrenals outgrow kidneys
24 weeks	Kidneys outgrow adrenals
32 weeks	Fetal cortex occupies 80% of gland
1 month of age	Adrenal cortex involute by 50%
6 months	Adrenal medulla enlarges
1 year	Adrenal gland weighs 1 gram
3 years	Fully differentiated gland

Physiology:

Hypothalamo-pituitary-Adrenal axis is essential for production and regulation of adrenal steroids. ACTH has a pulsatile release and more secretion is during the early morning hours. The production of ACTH is under the control of CRH (corticotriopin releasing hormone). CRH production is mainly increased by arginine vasopressin(AVP). Both AVP and CRH are also produced in the pulsatile fashion into the circulation. . In CAH, when this axis is disturbed the negative feedback is lost[4] and hence would result in increased production of ACTH and CRH. These abnormally elevated hormones have their effects on learning and memory through their action on amygdala[5-9]. The following flow chart shows the action of ACTH to increase the Adrenal steroidogenesis.



ACTH does not have much effect on the production of mineralocorticoids. Their production is mainly under the influence of rennin-angiotensin system.

Actions of glucocorticoids-

1. Increases gluconeogenesis and resistance to insulin and hence results in hyperglycemia.
2. It would also increase lipolysis and redistribution of fat resulting in truncal obesity [10,11] and moon facies when in excess.
3. Proteolysis causing increase in amino acid pool, which could be further used for gluconeogenesis.
4. They cause an increase in cardiac contractility and when deficient, decreases cardiac output.
5. Skeletal maturation is inhibited by glucocorticoids.
6. They decrease cellular immune response and hence are described to have anti-inflammatory action. They cause decrease in levels of inflammatory mediators.
7. Decrease serum calcium levels by decreasing absorption from intestine and increasing excretion in the kidneys and hence leads to osteoporosis.
8. Cause emotional lability[12-15] and disturbances in memory and cognitive functioning when in excess[16].
9. Glucocorticoids cause reduction in the levels of growth hormone and IGF-1[18] through complex interactions [17] and an increase in levels of

IGF BP-1(insulin like growth factor binding protein-1) and thereby have a direct inhibitory effect on epiphysis, when in excess.

10. Help in decreasing cerebral edema. They may have multiple psychological manifestations like euphoria, depression and psychosis.

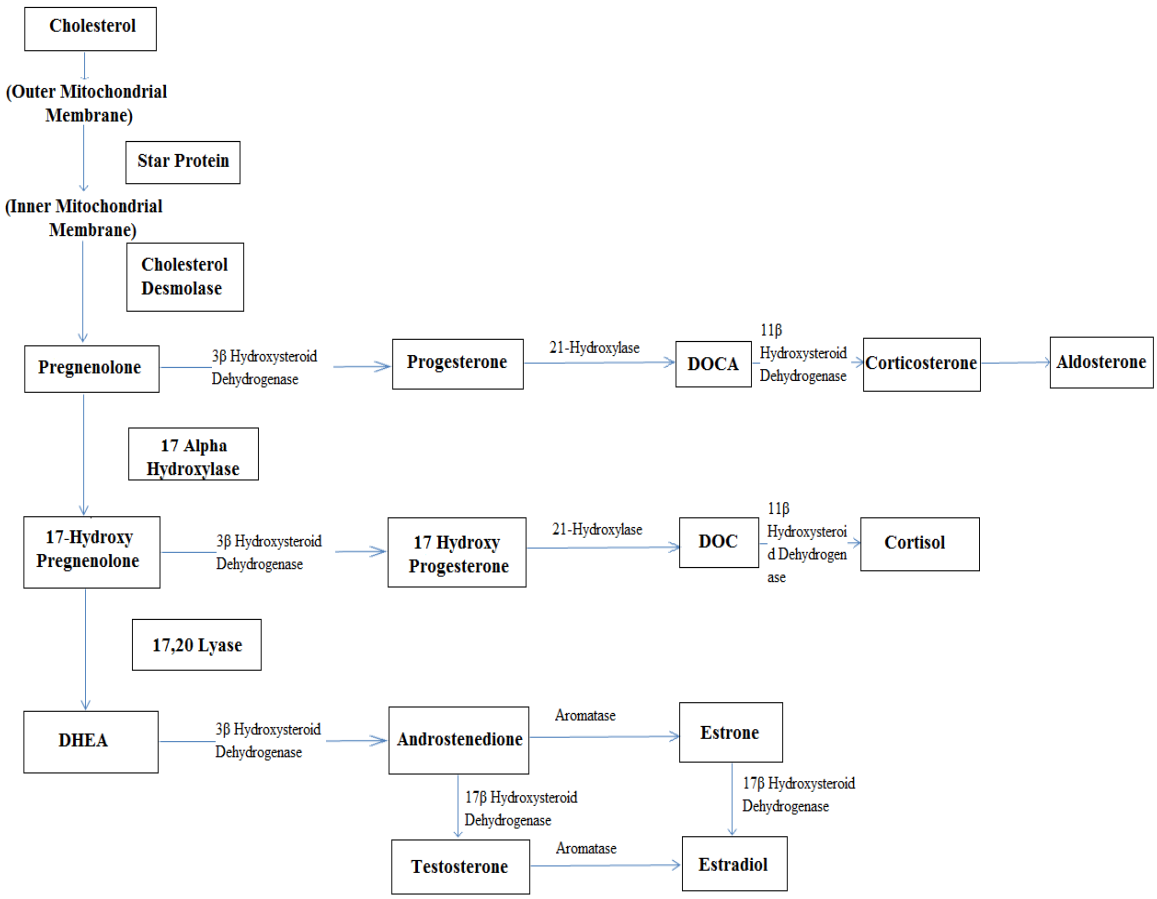
Actions of mineralocorticoids-

Mainly involved in reabsorption of sodium ions and excretion of potassium in the kidneys.

Action of androgens-

50% of androgens in women are from adrenals. Helps in development of secondary sexual characters like axillary and pubic hair.

Normal steroidogenesis pathway-



Congenital adrenal hyperplasia:

Adrenal gland enlargement in CAH was first described in 1865 by De Creuhio, an anatomist. Cortisol was used for its treatment first in the year 1950[19,20]. Adrenal gland hyperplasia in CAH would result from increased ACTH levels which is produced as a feedback from pituitary due to steroid hormones deficiency[4]. Deficiency of specific enzymes involved in steroidogenesis in the adrenal would result in lack of cortisol with or without aldosterone. This would also cause excessive production of precursors. These are then converted to androgens and would result in various clinical manifestations of the disease.

Most common enzyme deficiencies constituting CAH include-

1. 21-hydroxylase deficiency
2. 11-beta hydroxylase deficiency
3. 3-beta hydroxysteroid dehydrogenase deficiency
4. 17-alpha hydroxylase deficiency
5. 17,20 lyase deficiency
6. Congenital lipoid adrenal hyperplasia
7. P450 oxidoreductase deficiency

21-hydroxylase deficiency :

This is the most common enzyme deficiency constituting CAH. More than 90% of cases of CAH are due to this[1]. 21-hydroxylase is the enzyme involved in the hydroxylation of progesterone and 17-hydroxyprogesterone to 11-deoxycorticosterone and 11-deoxycortisol. These intermediate metabolites

are then converted to aldosterone and cortisol. Hence deficiency of 21-hydroxylase would result in both cortisol and aldosterone deficiency.

Classification:

21-hydroxylase deficiency may be of two types-

1. Classical
2. Non-classical

Classical type is again reclassified into

1. Salt wasting
2. Simple virilizing

Classical type:

Incidence of classical type is about 1 in 15,000 to 20,000 births[4,21]. Of the both varieties of classical type, salt wasting is the most common type which constitutes 70% of the total cases [1]. Both cortisol and aldosterone are deficient and hence would result in salt wasting crisis, if not identified and treated early. The mutations in salt wasting type leads to total absence of enzyme activity[22-26]. In addition to salt wasting crisis, symptoms of androgen excess may be there. On the other end, simple virilizers have their mutations which may retain up to 1 to 2% of their enzyme activity[27-29]. Hence their presentation will be mild and only symptoms suggestive of androgen excess alone may be there.

Non-classical type:

Non-classical variety has a prevalance of 1 in 1000. Hence it appears to be most common but goes undiagnosed in many. Amount of enzyme activity that is retained ranges from 20% to 60%[31-33] based on which the

characteristics may vary. In population groups like Ashkenazi jews, incidence may be as high as 1 in 27[30].

Inheritance:

CAH is a autosomal recessive disorder. There are two types of gene involved in the production of 21-hydroxylase enzyme. One is the active gene and the second one is a pseudogene. These genes are located in chromosome 6p 21.3[34] Three types of changes may occur among these genes resulting in the disease-

1. Most common being recombination between those two genes amounting to 90% of the total genetic defect [27].
2. Unequal meiotic cross-over between these genes.
3. Gene conversion.

Clinical features:

Because of the various degree of involvement of 21 hydroxylase, the spectrum of clinical features may be diverse[35]. Based on severity they are classified into

Salt-wasters:

Presentation may take even up to 1 to 2 weeks of life. Newborn may present with recurrent vomiting causing dehydration and hypotension. Other markers were hypoglycemia and dyselectrolytemia in the form of high potassium and low sodium levels. If not recognized and started on steroids it would result in shock and death. Female babies have ambiguous genitalia at

birth. Other clinical features may include hyperpigmentation in both male and female babies.

Simple-virilizers:

Only presentation may be ambiguous genitalia in girl babies. Hyperpigmentation may or may not be associated. Male babies present with hyperpigmentation and penile enlargement which may be missed in many[4]. Pseudoprecocious puberty may be there in some males[36,37].

Non-classical type:

Female babies may have normal genitalia at birth. They may later have precocious pubarche. Other mild symptoms like acne[38] and hirsutism may be there. They may also remain asymptomatic.

Hormonal changes:

1. The step which is blocked in this is the conversion of 17OHP and progesterone to aldosterone and cortisol. Hence it results in the accumulation of 17OHP. Further stimulating the production of ACTH, which would again try to increase steroidogenesis. Since there is a block, the precursors would accumulate and hence producing high levels of 17-hydroxyprogesterone. These are then shunted to androgen synthesis pathway.
2. These metabolites may act as mineralocorticoid receptor antagonist and would exaggerate the effects of mineralocorticoid deficiency. There had been evidences stating that some degree of aldosterone deficiency is always associated[39].

3. Development of adrenal medulla may also be affected because embryologically in the fetal period development of medulla needs exposure to excess amount of cortisol. Adrenomedullary dysfunction is thus mostly associated in 21 hydroxylase deficiency[40].

Effects of androgen excess:

1. As early as 8 to 10 weeks of gestation fetus would be affected because of androgen excess.
2. Female babies have clitoromegaly with or without labial fusion which is more severe in salt wasters[41]
3. Sexually dimorphic behavior in females.
4. Advanced bone age due to the rapid skeletal growth.
5. Early epiphyseal fusion and hence are short adults.
6. Early pubarche in both the sex.
7. External geniatalia in males may increase in size prepubertally. This constitutes only the penis and scrotum whereas testis may remain smaller.
8. Adrenal rest cancers (TART)[42,43] are rare.
9. Delay in thelarche and menarche in females.
10. Infertility in females [44-47].

Diagnosis:

1. Blood 17-hydroxyprogesterone levels would be elevated and it should be measured in the morning hours. Could be done on third day of life. Levels more than 240 nmol/l in suspected case is considered diagnostic

of 21 hydroxylase deficiency[41]. The levels of 17OHP are lower in simple virilizing than salt wasting type.

2. ACTH stimulation can be done for doubtful cases where following stimulation, 17 OHP levels are measured at 30 and 60 minute interval and plotted on normogram[48].
3. Blood electrolytes show hyperkalemia and hyponatremia. Acidosis with hypoglycemia may or may not be associated.
4. Plasma rennin levels may be elevated while serum aldosterone levels may be low.
5. Serum cortisol may be low but it is of low diagnostic value.
6. Karyotyping and ultrasonogram of abdomen should be done to rule out other causes of ambiguous genitalia.
7. Options for prenatal diagnosis include chorionic villous biopsy or amniocentesis for DNA analysis. Measurement of hormone levels in amniotic fluid can also be done[49].

Newborn screening-

First developed in 1970's, now established in many nations[50]. The estimated infant mortality rate in the absence of neonatal screening is 20-40%[51]**.** Here we measure the levels of 17OHP in the filter paper which are stained with blood spots from heel prick on day 3 of life[51,52]. Helps us to diagnose the disease even before occurance of adrenal crisis. If screening reports show equivocal or positive results it should be confirmed with venous

sample report. Main disadvantage is that this could not identify all cases of simple virilizing form and children exposed to steroids antenatally[53].

Management:

Replacement with deficient steroids is the mainstay in the treatment of congenital adrenal hyperplasia. This replaced steroids will breakdown the feedback and production of adreno corticotropic hormone decrease. Hence the production of androgens would also decrease. Dosage of glucocorticoids needed should be monitored from the period of starting the drug. Drug of choice is hydrocortisone because it is regarded to have minimal growth suppressing effects[54]. In the neonatal period as high as 20 mg/m^2/day[55] may be needed and this should be tapered slowly to a dose of 10-15 mg/m^2/day during infancy. Studies have shown the physiological cortisol secreting rate as 4.8 to8.7mg/m^2[56] which is lower than the previously accepted levels.

Steroids are administered as 3 divided doses in a day. Treatment should be continued lifelong for all classical type of 21-hydroxylase deficiency. Dose of drug should be increased during periods of stress. It may need up to double or triple the maintenance dose. But our therapeutic goal must be to use lowest steroid dose required for adequate androgen suppression. If followed strictly with good compliance and right dose it would result in a final height(FH) equal to target height(TH)[57]. Risk of obesity may also decrease with correct steroid dose[58].

Fludrocortisone replacement should be done for all patients with salt wasting type. Initially started at high doses 0.1 to 0.3 mg daily and should be

tapered to 0.05-0.1 mg daily. Fludrocortisone can also be used in non-salt wasting form, because it reduces the dosage of glucocorticoid needed[59]. Adequate salt supplementation during the first year of life will have improved outcome[60].Other drugs which could be used are flutamide (antiandrogen) and anastrazole (aromatase inhibitors). In some patients growth hormone replacement may be needed to improve adult height.

Surgical management:

For severe clitoromegaly, surgery is the choice of treatment. Partial excision of corporal bodies are done. Vaginoplasty and urogenital sinus corrective surgery may be needed in some patients and this is usually followed by a revision surgery at adolescence period.

Bilateral adrenelectomy[61] may be needed in adult females with severe hyperandrogenism at the risk of occurrence of Nelson syndrome.

Antenatal management:

After the diagnosis of the index child, all the subsequent pregnancies should be treated with dexamethasone at the dose of 20 micrograms/kg/day. This should be started immediately after the pregnancy is being confirmed and continued till term in case of female fetus. In case of male babies, treatment is discontinued after sex is confirmed. Dexamethasone is not inactivated by 11-beta hydroxysteroid dehydrogenase present in placenta and also it binds only minimally to cortisol binding globulin. The advantage hence is that it could cross placenta easily[62].Administration of dexamethasone is associated with maternal side effects like hypertension , diabetes and cushingoid features.

Other enzyme deficiencies:

The second most common enzyme deficiency constituiting congenital adrenal hyperplasia is 11-betahydroxylase deficiency. This includes 5% of the total cases. Due to this enzyme deficiency 11-deoxycortisol and 11-deoxycorticisterone are not converted into cortisol and aldosterone. There may be associated hypertension because of the increased levels of deoxycorticosterone acetate. Features of hyperandrogenism may co-exist. Diagnosis is mainly by demonstration of elevated levels of 11- DOC and DOCA. Treatment is with hydrocortisone and for hypertension with calcium channel blockers.

Next common enzyme deficiency is 3-betahydroxysteroid dehydrogenase deficiency. Hence here delta 5 steroids are not converted to delta 4 steroids. This constitutes 2% of the total CAH cases. Salt wasting crisis may occur. DHEA levels are elevated which may cause mild virilisation in girls and since it is a weak androgen it would also result in hypovirilised male. Treatment requires both glucocorticoid and mineralocorticoid replacement. Male children may require testosterone depot injection for phallic growth.

17- alpha hydroxylase deficiency constitutes less than 1% of cases. There is deficiency of androgens with increase in production of DOCA. Hence male babies are hypovirilised. There may be associated hypertension because of increased levels of DOCA. Treatment is with cortisol and antihypertensives. Estrogen replacement may be done at puberty.

Lipoid adrenal hyperplasia is due to the mutations in STAR protein gene. Hence here, cholesterol could not move from outer to inner mitochondrial membrane. This would result in cell death in adrenals and testes. In this disorder males are born phenotypicaly as females. This is due to the absence of production of androgens. Treatment is with glucocorticoids and mineralocorticoids. Replacement with estrogen at puberty may be needed.

There is another variant called as Antly-bixler syndrome where there is total absence of cytochrome p450 oxidoreductase enzyme, which is required for the action of all the above said enzymes. Hence they may have combination of features of all the above said enzyme deficiencies. In addition they have other features like frontal bossing, craniosynostosis, midface hypoplasia and brachycephaly.

CAH and its effect on physical growth:

Children with CAH have alterations in their growth pattern. The cause may be either hyperandrogenism or hypercortisolism when treated with excess steroids. In some children inspite of steroids used at so called physiological doses, there may be growth alteration. The reason quoted for the same is transient hypercortisolism immediately after the absorption of the drug which has been used for long term[63]. Other reason may be increased serum cortisol level upto a supraphysiological doses during initiation of treatment, in the first year of life. This is the main cause for the delayed bone maturation and short stature in the adult life.

Other cause quoted was that the inadequate suppression of hyperandrogenic state which may advance the bone age in children but ultimately cause early epiphyseal fusion resulting in short stature among adults. Other reason for early epiphyseal fusion in some may be due to central precocious puberty[64]. There had been a metaanalysis which showed mean final height in adults was -1.37 SD[65]. Glucocorticoid replacement therapy would cause reduction in height and osteoporosis in later life when used in higher doses than recommended.

There had been recommendations for normal pubertal development and in a recent study it has been quoted that the dose of hydrocortisone should not exceed 17 mg/m^2[66]. At the same time hyperandrogenism would also result in advancement of bone age and its consequences. There are also differences in the type of disease. This is because salt-wasters are diagnosed early and started on treatment early and are said to have better outcomes as far as physical functioning is considered. But, 25% of classic CAH have salt-wasting crisis which may influence on the final height.

Hence it can be concluded that final height is influenced by number of factors:

1. Age at diagnosis
2. Dose of steroid
3. Adequacy of treatment
4. Type of CAH

Studies have stated that though clinical examination is the most efficient way of monitoring the adequacy of treatment, but still day to day changes could not be reflected and hence it is recommended to use biomarkers like androstenedione for perfect monitoring.[67] For these patients, whom there had been a reduction in growth, treatment with short term growth hormone replacement and GnRH analogue would result in a growth of about 11 cm than expected[66]. Selection of patients for such a treatment is based on presence of psychological stress and adjustment difficulties owing to their short stature.

CAH and effects on social functioning:

CAH is a disorder where female babies are born with excess of male sex hormones and hence naturally a sexual dimorphic behavior could be expected from these girls. There are certain personality traits which are specific for a particular sex. For example traits like dominance and assertiveness are more specific for men whereas tender mindedness and empathy are more specific for girls[90]. Hence in conditions causing hyperandrogenism as in CAH, there had been modifications in these behaviors. Increased male pattern behavior and increased aggressiveness may occur in these groups of children. There had been studies quoting that early hormonal environment is one of the most powerful determinants of sex differences in personality. Affected girls especially have increased tendency to have a male playmate, male activity preferences and increased tendency to fight and physical aggression [68].

But studies have shown mixed results when aggression in CAH children is evaluated. Some have stated increased aggression[69], while some have

quoted no significant association between CAH and aggression[70]. Aggression in these children may also be due to the sexual precocity[71]. Androgen excess in the early periods of brain development will affect the neural differentiation, cell survival and neural connectivity and neurochemical characterization[72].

There are also proved evidences stating increased incidence of psychiatric disorders like autism and attention deficit hyperactive disorder in these children[73]. This may be again because of the hyperangrogenic state. In general males tend to have more incidence of psychiatric disorders owing to their natural androgenic state[74]. Previously studies have done to prove the intrauterine hyperandrogenic states by measuring the levels of testosterone in amniotic fluid which showed a perfect positive correlation with the male typical behavior in girls.

There had been a lot of confusions regarding the Gender role/identity problems where some authors state that there is problem while others state that cognition and Gender role identity are not affected.

Early androgen exposure has also lead to the predisposition of these children to specific learning disabilities[75]. There are multiple domains in which a child with CAH may have deficit including communication, socialization and daily living skills. Physiological cause for these increase in aggression and male typical behavior is increase in androgen receptors in medial amygdaloid nucleus in children having high prenatal androgen exposure. In many studies it has been quoted that when these children are exposed to a negative situation, amygdale would be hyperactive than a normal

person. Melanocortin-4 receptors are mainly involved in the modulation of anxiety and depression like behavior in Amygdala. CAH is also associated with increased ACTH and CRH. These hormones would act on these receptors situated in amygdala and cause psychiatric symptoms and aggression.

Another interesting thing to note is that males do not show an increased aggression. This is because of the feedback mechanism which would reduce the androgen synthesis in response to the excess adrenal androgens[76].

There are a number of scales for the measurement of social adaptive behavior and the most commonly used and valid scale is vineland social adaptive behavior scale, which is used in our study.

CAH and cognition:

Cognition includes process of thinking, reasoning, memory, comprehension judgement and problem solving. There are innumerable number of studies stating that steroid hormones influence cognitive functioning [76]. Cognitive functioning and intelligence is directly related to social Adjustment and Aggression [77]. As these group of children have social Maladjustment and aggression[78], Intelligence assessment becomes essential. There are innumerable scales for assessment of intelligence quotient:

1. Wechsler's intelligence scale for children
2. Malin's intelligence scale for Indian children[79]
3. Binet-kamath test
4. Seguin-form board test
5. Wais adult intelligence scale.

And scores based on which cognitive impairment can be categorized in to:

1. 90 to 110 –normal
2. 70 to 89- borderline impairment
3. 50 to 69- mild impairment
4. 35 to 49-moderate impairment
5. 20 to 34- severe impairment
6. < 20- profound impairment

Congenital adrenal hyperplasia is the condition which carries the risk for both hormonal imbalance starting from the intrauterine life and steroid treatment both of which may have an effect on cognition. But studies are inconclusive in CAH as far as cognition is concerned[77]. Malouf et al [80] done a study to detect cognitive assessment but failed to detect Intellectual Impairment. Some studies have even quoted IQ advantage in these patients[81]. Reason for this IQ advantage was stated as increased androgen levels and their complex interactions with brain.

But, other studies have quoted that high androgen levels were shown to impart changes in the synaptic plasticity in hippocampal CA1 cells in juvenile rats[77]. In the same study it also been clearly stated that elevated androgens may reduce social cognitive performance. Androgens also delay cerebral maturation in the prenatal and perinatal periods especially of the left cerebral hemisphere which would lead on to abnormalities in neuronal migration or abnormal connectivity[82]. High levels of ACTH levels may also reduce the

emotional learning and memory[77]. This action is exerted mainly through their action on melanocortin receptors in amygdala. Studies have also quoted decreased amygdale volume in CAH patients[87].

Steroids used for the treatment of CAH can exert their effect on cognition through 2 ways-

1. Organizational alteration and

2. Activational alteration.

Organizational effects include permanent changes in the brain structure (hippocampus and amygdala) inutero[77]. Activational effects include acute effects of circulating steroids in the later age. Some have told that there is neural degeneration of hippocampal pyramidal neurons and reduced hippocampal glucocorticoid gene expression based on the study done on rats [84]. This is associated with increased anxiety behaviors and problem with spatial cognition.

Children with salt-wasting type have lower intelligence quotient compared to simple virilising type [80]. The cause may be due to the diffuse brain injury during episodes of hypotension and hyponatremia which would further impair their IQ. There had been documented white matter lesions in MRI leading to visuo-spatial impairment which is essential for solving arithmetic problems[85]. Hence, their visuospatial and cognitive skills are also poor.

REVIEW OF LITERATURE

There are only limited studies dealt with congenital adrenal hyperplasia and its effects on growth, social behavior and cognition.

Rose Girgis et al conducted a study in the year 1997 at Alberta university at Canada and he recorded the effects of glucocorticoid replacement in congenital adrenal hyperplasia[86]. Parameters studied were growth, bone mineral density and bone turnover markers in these children. He did the study on 28 CAH patients who were on oral cortisol 10 to 15 mg/m2/day for about 4.7 to 22 years.

He classified patients into three groups based on 17 OHP levels as tight control(<10 nmol/L), fair control(10-40 nmol/L) and poor control(>40 nmol/L). They found that there had been not much of difference in the height which was plotted on a standard Z- score chart. The height Z scores were plotted for present height, height at 2 years of life and growth velocity. But, a significant difference was observed in the bone maturation Z-score. It was about -1.63 in tight control group and +0.8 in poor control group.

Finally concluded that delayed bone maturation is seen in children who received high dose of steroids and hence resulted in tight control of 17OHP levels. Hypercortisolemia during infancy would lead on to significant height reduction.

Vickie Pasterski et al[76] conducted a study in the year 2007 at university of Cambridge with 38 girls and 29 boys with CAH (age group- 3 to

11 years). Control group was their unaffected siblings (25 girls, 21 boys). Activity Level/Extraversion Questionnaire was given to mothers to indicate aggressive behavior and Hyperactivity in these children. The questionnaire had 17 items which was actually extracted from a temperament questionnaire. Results showed that (as per Maternal Reports) Males are more aggressive than Females.

Analysis of Co-Variance showed sex and disease process interaction ($F=13.49$, p value of <0.001). Boys without CAH were found to be more aggressive than girls without CAH, ($t=4.22$ $p < 0.001$), whereas CAH girls were found to be more aggressive than unaffected girls ($t= 4.25$, $p <0.001$) and finally both boys and girls with CAH and unaffected boys never differed from each other. For activity level, results showed boys without CAH are more active than girls without CAH, $t= 2.01$, with p value corresponding to 0.013, affected girls are more active than girls without CAH, $t=2.15$, with p value of 0.009. Hence finally hypothetised that:

1. Boys are more active and aggressive than girls.
2. Affected girls are more active and aggressive than unaffected girls.
3. Aggression and Activity level shows no difference between CAH affected and unaffected males.

A case-control study was done at a pediatric endocrinology centre in the year 2006 at Copenhagen university hospital by Trine H. Johannsen and Caroline P. L. Ripa et al to demonstrate the impairment of cognition in these patients. Subjects were selected from 17 to 51 age group[78]. Totally thirty five

women were selected. Age and education matched controls were selected. Weschler adult intelligence scale showed decrease in cognition levels in the affected women compared to the normal controls.

Mean intelligence quotient levels were demonstrated to be around 84 whereas in normal controls it was around 99.1 ($p < 0.001$). Among the affected CAH patients it was the salt wasters who had lower IQ than simple virilizers. It was 81.2 in salt wasters and 92.8 among simple virilizers, and was statistically significant.

The causes stated were recurrent episodes of hyponatremia, improper postnatal hormone replacement therapy, androgen excess in the prenatal period and also the psychosocial effects of the disease process.

Francoise S. Maheu et al conducted a study at National Instituite of Mental Health at Bethesda in the year 2008, to demonstrate the effects of steroid abnormalities on the developing brain[77]. They analysed the declarative memory in CAH children by making these children recall the emotionally arousing picture already shown to them. Author has clearly stated that steroid hormones modulate memory in humans. They have used this disease as a natural model for demonstrating the effects of steroidal abnormalities on memory. They have included totally 34 children in to the study. Seventeen of them had the disease whereas the remaining seventeen normal matched one were controls. Age group studied was between 12 to 14 years.

These children were presented with three types of pictures. One was positive, second one was negative and the third one was a neutral picture.

Memory recall of all these pictures were done after about 30 minutes. Results finally showed that children with congenital adrenal hyperplasia demonstrated a significant lack in memory especially for negative pictures compared to healthy children. The p value was < 0.01. But for the other group of pictures, significant p value could not be demonstrated.

Other secondary outcomes which was established in the same study includes demonstration of no association between 24 hours free cortisol levels, testosterone levels and memory performance. Hence finally it was concluded that early steroid imbalances would result in deficit of memory for emotionally negative stimuli. The cause for this memory impairment was stated as abnormal brain organization resulting from Hormonal Imbalances during vital phase of brain development.

S.C. Muller et al have conducted a study in 2008 at National Institute of Mental Health at Bethesda to prove the fact that early androgen exposure would change the spatial cognition level in patients with CAH[83]. Since CAH is a natural model for early androgen exposure, patients with this disorder were enrolled in to the study from NIMH at Bethesda. Age and sex matched controls were selected. Total of 54 CAH patients were compared to 55 unaffected population. CAH patients were divided into three different groups. First group contained 25 salt wasters, second one with 13 simple virilizers and third group with 16 patients belonging to non-classical type of disease. 55 age and sex matched controls were selected. Anthropometry and x-ray for bone age were done. Anthropometric values did not differ among groups whereas

bone age was slightly more advanced in in salt wasters than simple virilizers. Hormonal levels (17 OHP and testosterone) were measured prior to a virtual task which is equivalent to morris water maze was used and their spatial cognition was compared.

Results indicated that two variables, severity of the disease and the period of exposure of androgens are significant. It is concluded that more severe form of disease in the females and more periods of androgen exposure in females have resulted in improved spatial cognition.

Sven. C. Mueller et al by the year 2010 conducted a study in NIH, Bethesda hospital to evaluate for the psychiatric morbidities in children with hyperandrogenism[87]. Hence two diseases were included- CAH and familial male precocious puberty(FMPP).

Children between 8 to 18 years were selected it mounted to totally 72 children of which 54 were CAH and 18 were FMPP. Psychiatric interview which was a semi-structured was conducted for all these children. The interview was mainly based on the kiddie schedule for affective disorders and schizophrenia- present and lifetime version.

Based on this, results revealed about 44.4% of CAH patients and 55.6% of FMPP patients had atleast one time diagnosis of some psychiatric disorder in their life. Among these psychiatric disorders ADHD was more common and being reported in 18.2% of CAH male patients and 44.4% of FMPP patients. Anxiety disorders were also reported (17 to 21%).

Hence it was finally concluded that, although psychiatric illness may accompany any chronic illness, hyperandrogenism has been associated with increased incidence of Psychiatric Disorders. Psychiatric assessment should thus be a part of routine evaluation for all, these patients.

A cross-sectional study was conducted among the CAH dutch population in the year 2012 to assess the quality of life in these patients [88]. Self-designed questionnaires which is mainly based on the Netherlands questionnaire were used. Study totally enrolled 106 patients.

They were divided into three groups based on age. First group included children between 0 to 4 years, totally 12 children in this category. Second group included 63 children between 4 to 12 years and the third one included 32 children between age groups 12 to 18 years.

Totally four different questionnaires were prepared. One questionnaire for parents of each group and fourth one for 12 to 18 year children. About 75% of children were salt wasters in 0 to 4 years group. About 79% were salt wasters in adolescent group. 33% of adolescents had not experienced any health related issues. 33% experienced more than 4 daily health related problems.

Parents mentioned weight loss, excessive sleepiness and reduced appetite as the most common health related problem. About 31% had complications due to the disease in the neonatal period. 71% experienced daily health daily problems in the past two weeks. Children in the age group of 4 to

12 experienced more health related issues. Adrenal crisis was reported in 33% of children.

However in total 96% of the parents were found to be satisfied with the overall health. Two scales were actually used in the study. They were experiences parents scale and difficulties scale. Scores were found to be slightly more than three which means a positive influence. 82% of the children use 2 medicines regularly. From the results obtained it was finally concluded that these children and adolescents are able to manage their own problems at a young age. But on the daily basis they may experience some health related issues. Affected children also participate well in all school and leisure activities. Only few of them carry a crisis card with them. Hence CAH children face only few negative effects because of the disease.

Greta A. Mathews et al conducted a study at Middlesex and great ormand street hospital in London in the year 2009 to determine the influence of early androgen exposure on the personality traits[90]. Totally 128 participants, between age group 12 to 45 years were recruited into the study and were divided into four groups.

1. CAH affected females(n=40)
2. CAH affected males(n=29)
3. Female controls(n=29)
4. Male controls(n=30)

Parameters which were mainly studied include that of tender mindedness using 16 personality factor inventory, aggressiveness using reinisch aggression

inventory and interest in infants based on melson's questionnaire and dominance again based on personality factor inventory. Results showed that tender- mindedness is less among affected females with a significant p value of <0.001.

Greater physical aggression was reported among CAH girls compared to their normal peers ($p<0.05$). Interest in infants is less for CAH women ($p <0.001$). In males who are diseased, their interest in infants does not show a significant difference. But it has been showed that males with CAH are more tender minded than their peers with a significant ($p < 0.05$). They were also less dominant ($p<0.05$). Physical aggressiveness is less compared to controls ($p<0.05$).

Hence it was finally concluded that prenatal androgen exposure can alter some of the female characteristics in to a more male typical behavior. In males it is associated with a decrease in the expected male typical behavior.

H. J. Vander Kamp et al did a retrospective longitudinal study [60] in the year 2002 with 60 CAH patients on treatment with hydrocortisone and fludrocortisones. 34 salt wasters and 26 non-salt wasters were examined totally. Age group included was from 0 to 18 years. Author wants to study the alteration in growth patterns and puberty in these children. Recent dutch reference values were used for comparison.

Growth in the initial three months of life had shown a great difference when compared with the normal data. The mean length standard deviation

score was decreased to -1.50. The reason which is quoted for the same is high average steroid dose which may go even upto the levels of 40 mg/m^2/day.

They have also calculated the final height corrected for the target height (FH corrected for TH). Values of standard deviation score was -1.25 for females and -1.27 for males. Among these group, patients who are treated with adequate salt supplements were found to have better outcome. Their FH corrected for TH was -0.83 standard deviation score. Second group of patients (non-salt wasters) showed a standard deviation score of -0.96 in females and -1.51 in males.

The age of onset of puberty was compared between these two groups. But it was within normal limits in both. Bone age scores at the onset of puberty showed advancement of approximately 2.3 years compared to the reference values. Body mass index was compared which showed that in salt wasters BMI was not significantly different when compared to reference values. In non salt wasters, during childhood period mean BMI was not increased but BMI calculated for final height showed a significant increase especially in females with a p value of < 0.001 comparing with reference values. Hence it was finally concluded that the loss of final height potential in salt wasters is mainly because of excess of steroid doses used during infancy.

In case of non salt wasters loss of final height potential is because of delayed diagnosis. Advanced bone age at puberty is the main cause for loss of final height at puberty. Hence it is suggested that neonatal screening and early diagnosis and treatment is needed for expected outcome in these patients.

Ivani Novato Silva et al conducted a randomized controlled trial in the year 1997 to determine the effect of hydrocortisone on growth in congenital adrenal hyperplasia [89].

RCT was conducted for a period of 12 months. Totally 26 children were included under the study. They are randomly allocated into two groups. One group administered drug at 15 mg/m^2 dose and the other group treated with 25 mg/m^2. The age group ranged from 3.6 months to 15 years with median of 45.3 months. Age at diagnosis ranged from 0 to 79 months.

Each child were evaluated every 3 months by the same physician and measured height, growth velocity, weight, virilization or signs of steroid excess. 17 OHP, testosterone and androstenedione levels were also measured at each visit. F statistics was applied to evaluate the carryover effect of first treatment over the second one. Paired student's t test was used for comparison. Mean height and weight z scores at the beginning of the study was not much different. During the study it was observed that in the group receiving 15 mg/m^2 there was increase in height compared to the other group which is statistically significant with a p value of 0.02.

Growth velocity and 17OHP conceytrations were positively correlated. Growth retardation due to other causes like growth hormone deficiency was ruled out based on stimation tests like clonidine stimulation test and insulin like growth factor levels were also determined. Fludrocortisone withdrawal not caused any difference in non-salt wasters. Hence it was finally concluded from

the study that a higher dose of hydrocortisone used in children would depress the growth.

Treatment goal should not be set at full suppression or even normalization of 17OHP levels but should be set at normal growth pattern with no features of steroid excess. From the study it was also noted down that even very high doses of hydrocortisone (25 mg/m^2) were not able to suppress adrenal production of 17OHP in more than 50% of times. Hence it is always better to clinically correlate the laboratory values while follow up in congenital adrenal hyperplasia patients.

AIM OF THE STUDY

To study the physical, social and cognitive functioning in children with congenital adrenal hyperplasia on treatment.

OBJECTIVES

Primary objectives:

1. To study the physical functioning in children treated for CAH.
2. To study the social Adaptive behavior in CAH children.
3. To determine cognitive functioning (IQ) in CAH children.

Secondary objectives:

1. To determine the prevalance of aggression and ADHD in CAH children.
2. To compare salt wasters and simple virilizers in various aspects.

STUDY JUSTIFICATION

The treatment goal in congenital adrenal hyperplasia is to attain normal growth and development by judicious dosing of glucocorticoid and mineralocorticoid and close monitoring to avoid under- and over-treatment.

To meet the balance between too little or too much steroids is the major challenge especially in children with varied growth potential.

The evidence suggests that even if well treated, final adult height is a little shorter than what would have been predicted if they had not had the disorder.

Recent studies suggest that children with CAH also suffer from behavioral and cognitive disorders.

Since there had been very few studies on behavioral and cognitive functioning in India we proceed on with this study

METHODOLOGY

Design of the study : Descriptive study (cross-sectional).

Place : Pediatric Endocrinology department & Department of child guidance clinic, Institute of Child Health,

Period of the study : February 2015 to august 2015

SAMPLE SPECIFICATIONS

Case definition : All clinically and biochemically confirmed cases of congenital adrenal hyperplasia on treatment.

Inclusion criteria:

All children from 2 to 12 years who were diagnosed as CAH and on treatment.

Exclusion criteria:

- Other causes of growth abnormalities: familial short stature, growth hormone deficiency, nutritional causes, chronic systemic diseases.
- Chronic medications unrelated to CAH.
- Known psychiatric illness.

Sample size:

All children with above inclusion criteria who presented during the study period.

CONFLICT OF INTEREST : Nil

FINANCIAL SUPPORT : Nil

Ethical committee clearance was obtained from the institutional review board.

Maneuvre:

Children of age 2 to 12 years diagnosed to have congenital adrenal hyperplasia and satisfying the inclusion and exclusion criteria were recruited into the study, after obtaining informed parental consent.

Subjects with CAH those satisfying the inclusion and exclusion criterion were enrolled in to the study

Detailed history and old record analysis to look for the following:

- Type of the disease-Salt wasting or simple virilising
- age at diagnosis
- consanguinity
- siblings affected or not
- antenatal history
- social and demographic data
- Period of drug intake
- Compliance
- Dose adjustments
- Hospital admissions and school absentism

Anthropometric measurements:-

Height, Weight, BMI calculation and they are plotted on standard charts and assigned proper Z-scores

Blood pressure measurement:-

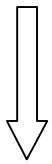
Both systolic and diastolic checked thrice (on three different occasions) and average of the three taken.

Sexual maturity rating is done for all children as per tanner's staging. Features of steroid excess - cushingoid features, obesity, hypertension, striae, hepatomegaly were noted. Systemic examination done to rule out all other causes.

Investigations:-

Radiological- X-Ray for bone age done

Biochemical- levels of 17-hydroxyprogesterone done



Pscychological assessment:-

- Social adaptive behavior from vineland social adaptive behavior scale
- Child behavior check list to look for any aggressiveness/ADHD

- IQ assessment using

  Gesssel's for children between 2 to 3 years

  BKT test for children 3 to 6 years

  Malin's intelligence scale for Indian children (MISIC) for more than 6 years.

Materials

Details of patient:

Details like age at diagnosis, type of disease, dose of Hydrocortisone for the last 6 months, duration of treatment, consanguity and sibling history were obtained from the records in our endocrine department.

Anthropometry:

Height for age:

Standing height is measured in stadiometer with occiput, shoulders, buttocks and heels touching against the vertical board. Head is positioned in Frankfurt plane. Height for age is obtained by plotting (accurate z score) in the standard growth chart. Recent WHO growth chart 2015 is used for children less than 5 years. 2015 IAP growth chart is used for children above 5 years of age.

Weight for age:

Weight for age is obtained by plotting in the standard growth chart same as height. WHO growth charts used for children less than 5 years and IAP growth charts are used for children more than 5 years.

Body Mass Index:

BMI is calculated from the formula weight in kilograms / (height in metre)^2. Calculated BMI is plotted on a standard growth chart and patients are divided into obesity (>3 z score), overweight (2 to 3 z score), normal for age (2 to -2 z score) and underweight (< -2 z score).

Blood pressure:

Blood pressure is measured using sphygmomanometer with patient in sitting position thrice. And the average of all the three values are taken. Both systolic and diastolic BP are plotted on NHBPEP (National High blood pressure education program, 2004) normogram.

Sexual maturity rating:

Done using tanner staging. Totally 5 stages are included and is separate for both girls and boys.

For girls:

Stage	Breast	Pubic hair
1.	Pre-pubertal	Pre-pubertal
2.	Breast nodule	Sparse long hair over labia majora, minimally pigmented
3.	Elevation of breast and areola	Dark curled hair over medial mons
4.	Secondary mound of areola and papilla	Adult type of hair over mons
5.	Adult(projection of papilla alone)	Adult type hair over medial thigh

For boys:

Stage	Testis	Scrotum	Penis	Pubic hair
1.	<4 ml	Pre-pubertal	<3 cm	Nil
2.	4 -10 ml	Reddening	3-6 cm	Sparse long over base of penis
3.	10-15 ml	Increased reddening	Increased length	Increased number and darkening
4.	15-20 ml	Dark (pigmented)	Appearance of glans, increased width	Spread around thigh
5.	>20 ml	Adult	Adult	Adult type of hair distribution

Features of steroid excess:

Clinical examination done and features suggestive of steroid excess like upward shift of weight percentiles, edema and cushingoid features were observed.

17 hydroxy progesterone:

17 hydroxy progesterone levels were measured from the serum of the patients collected at 8.00 A.M sample. 17 OHP estimation was done at hitech laboratory using radio-immunoassay. Normal values were reported to be in between 0.59 to 3.44 ng/ml.

X-ray for bone age:

Bone age assessment done from x-ray of pelvis, knees, left wrist, left elbow, following a standard chart at radiology department of institute of child health and hospital for children, Chennai.

Social adaptive behavior:

Vineland social adaptive behavior scale is used for obtaining a composite score which roughly corresponds to the social quotient. Sub-domain

raw scores are computed from identification of basal item and ceiling item. Domains include receptive, expressive, written language, personal, domestic, community communication, daily living skills and socialization. Standardized scale score (V Scale score) is determined based on age and domain standard score is then obtained. Then sum of all these domain standard score is obtained. Based on this scoring social adaptive levels are classified as:

Adaptive level	**v-scale**	**Standard score**
Low	1 to 9	20-70
Moderately low	10 to 12	71-85
Adequate	13 to 17	86-114
Moderately high	18 to 20	115-129
High	21 to 24	130-160

Classification	Standard score
Mild deficit	50-55 to approximately 70
Moderate deficit	35-40 to 50- 55
Severe deficit	20-25 to 35-40
Profound deficit	Below 20 or 25

Child behavior checklist:

CBCL estimates the externalizing disorders and internalizing disorders in children. It classifies them into normal range, borderline and in clinical range based on the scores obtained. Separate list of questions for boys and girls and also for children less than 6 years and more than 6 years exist in CBCL. somatic problems, anxious/depressed/ withdrawn, social, thought problems, attention problems, hyperactivity, rule breaking behavior and aggressive behavior were included. In our study aggression is given importance and concluded either child is aggressive, borderline aggressive or normal.

Gessel's Child Behaviour Schedule:

From the age of 4 months the child's development can be assessed based on Motor development, language development, adaptive behavior and personal-social behavior. The developmental age and its corresponding development quotient can be derived. In this study for children between 2-3 yrs this test is administered.

Binet kamath test for general mental abilities:

Binet kamath test is applied to all children above 3 years of age for obtaining intelligence quotient. For each age, 6 standardized questions are present and based on the child's performance their mental age is calculated. Basal age (where all 6 items are correct) and terminal age (where all 6 items are failed) is calculated. Mental age is calculated from the number of items which are being answered between the two basal and terminal age. In this study children between 3 – 6 yrs this test is administered.

Malin's Inteligence Scale for Indian children:

Malin's test is applied to children from 6 to 15 years of age for IQ; in this study age group of 6 to 12 yrs this test is done. This is an Indian adaptation of Wechler's intelligence scale for children. Full scale IQ comprises of 11 subsets – 6 for verbal intelligence which includes information, comprehension, arithmetic, similarities, vocabulary and digit span. 5 for performance intelligence which includes picture completion, picture arrangement, block design, object assembly, coding and mazes.

Statistical Methods:

The history, anthropometry, physical examination findings, laboratory investigations were collected from the children included in the study and recorded in data collection form. The data entered in the excel sheet. Data analysis was done by using epidemiological information package in computer. Frequencies, means, percentage, standard deviations, fisher's exact test, co-efficient of correction values and p value were calculated by using SPSS software frequencies.

OBSERVATION AND RESULTS

Totally 55 children with CAH on treatment were studied in the age group between 2 to 12 years.

Demographic characteristics:

Total number of females - 45

Total number of males - 10

Table 1 : Sex distribution of study population

Gender	N	%
Male	10	18%
Female	45	82%
Total	55	100%

Hence, 82% of our study populations were females and only the remaining 18% were males.

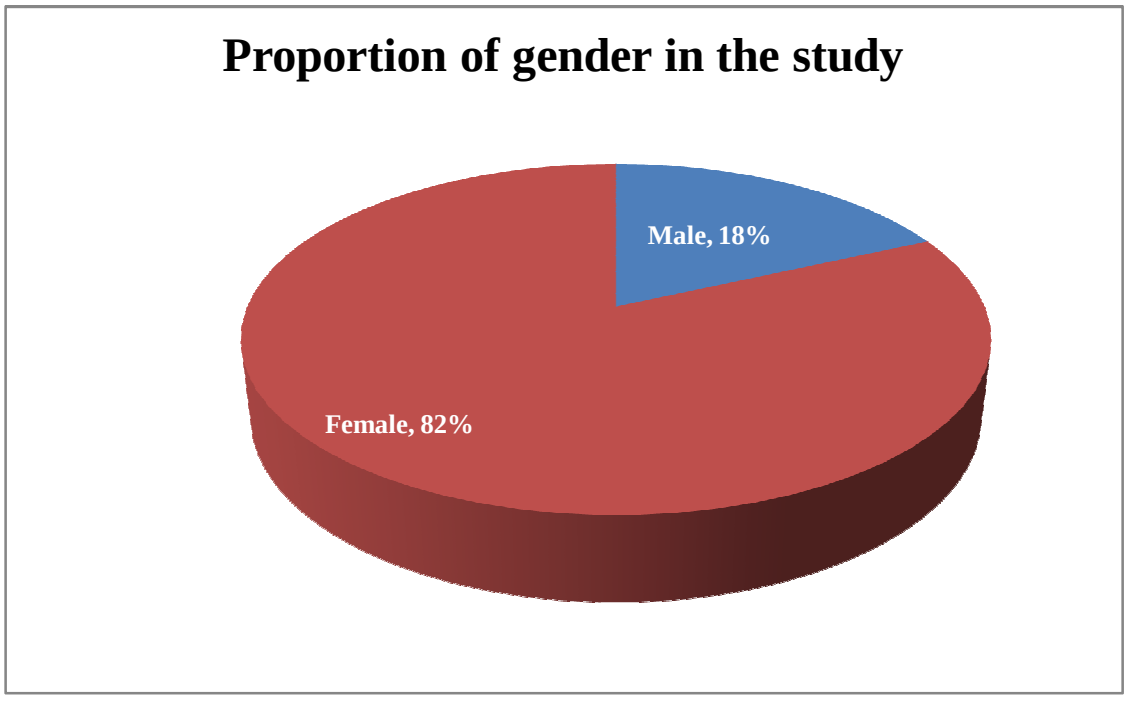
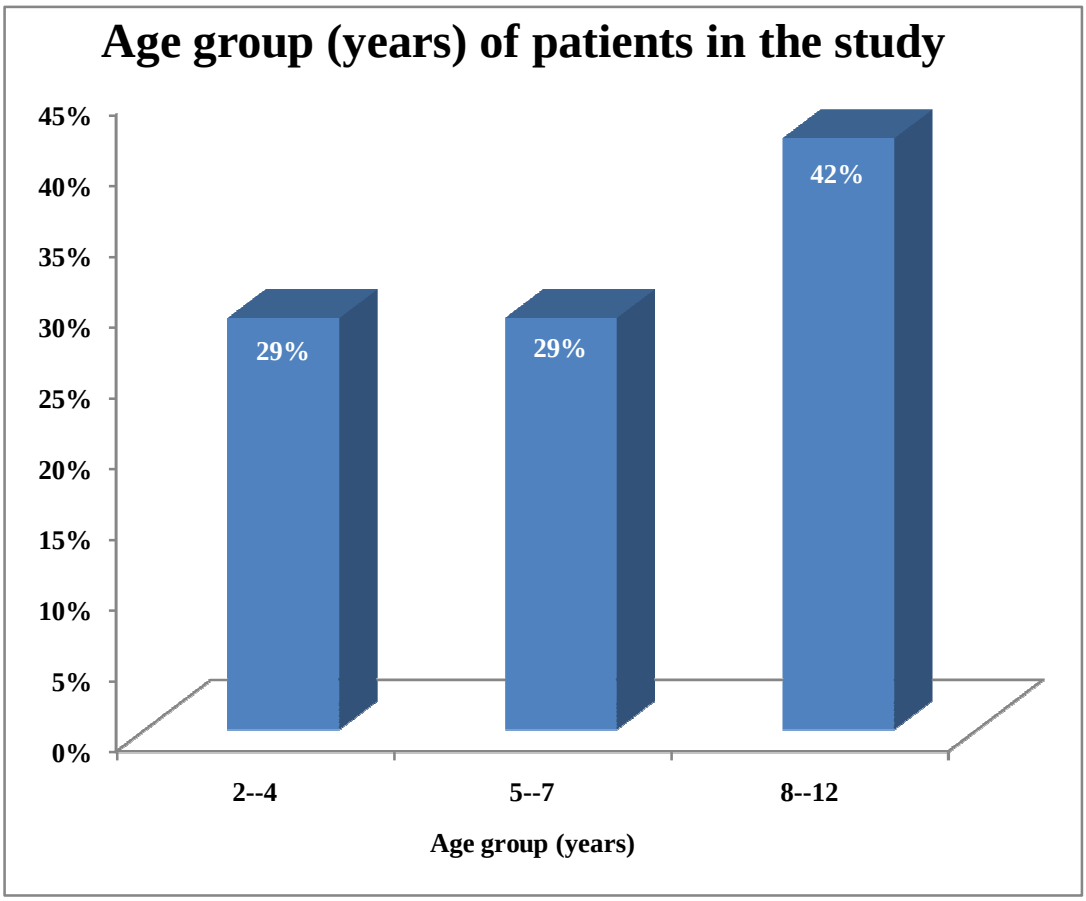


Table 2 : Age distribution of study population

Age group in years	N	%
2-4	16	29%
5-7	16	29%
8-12	23	42%
Total	55	100%



42% of our total population were between 8 to 12 years. 29% of them were between 2 to 4 years and 29% of them were between 5 to 7 years.

Table 3 : Age and sex distribution of study population

	Gender			Fisher's exact test
Age in years	**Boys**	**Girls**	**Total**	
2-4	2 (20%)	14 (31%)	16 (29%)	p value 0.436
5-7	2 (20%)	14 (31%)	16 (29%)	
8-12	6 (60%)	17 (38%)	23 (42%)	
Total	10 (100%)	45 (100%)	55 (100%)	

Among girls 38% were between 8 to 12 years, whereas among boys 60% were between 8 to 12 years. Between 5 to 7 years 20% of the total boys and 31% of the total girls were included in the study. The difference was not statistically significant.

Table 4 : Distribution of age at diagnosis of CAH

	Gender			Fisher's exact test
Age at diagnosis	**Boys**	**Girls**	**Total**	
Neonatal	6 (60%)	40 (89%)	46 (84%)	p value 0.078
Later	4 (40%)	5 (11%)	9 (16%)	
Total	10 (100%)	45 (100%)	55 (100%)	

In our study population, 84% of them were diagnosed in the neonatal period during salt wasting crisis and only 16% were diagnosed later. The difference is not statistically significant with a p value of 0.078.

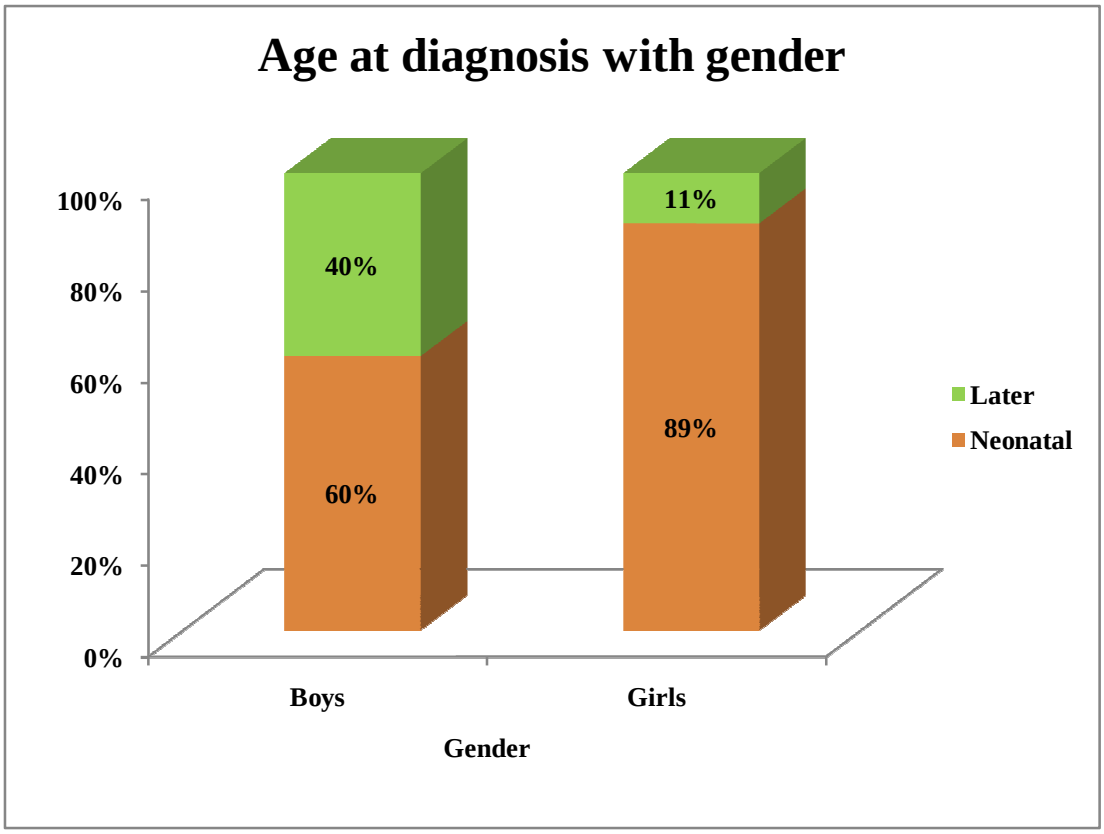
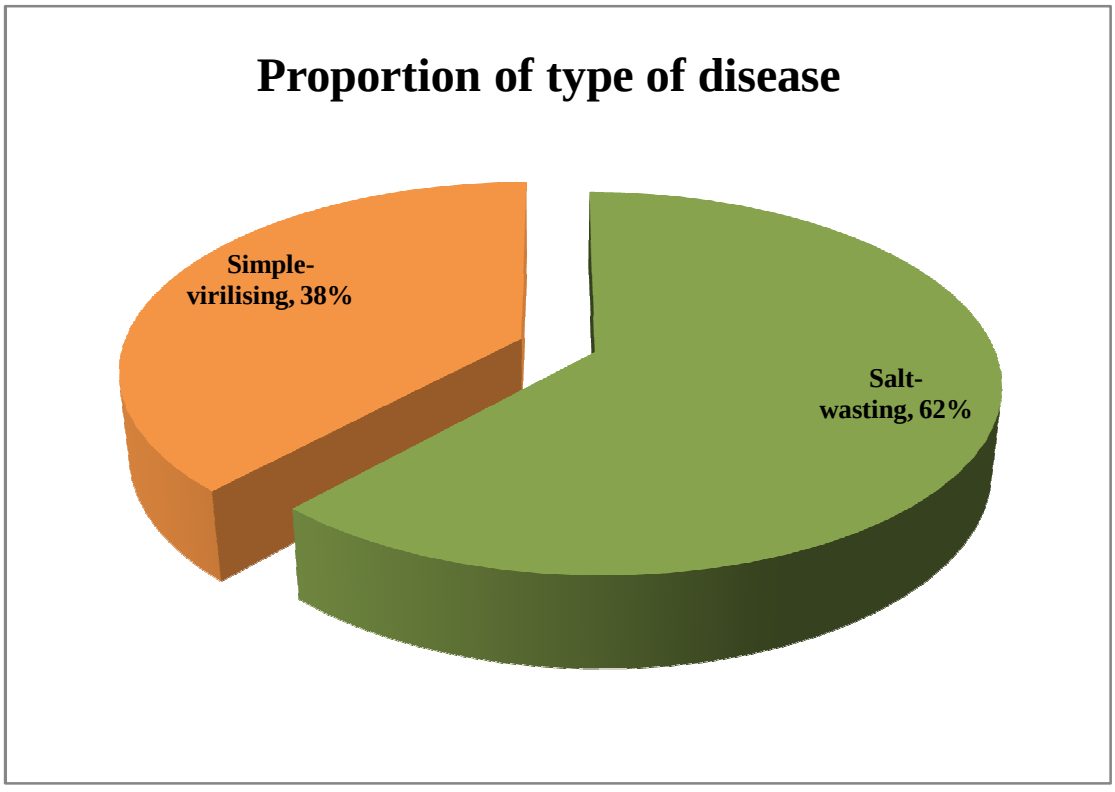


Table 5 : Distribution of type of disease between the two gender

Types of disease	Gender			Fisher's exact test
	Boys	Girls	Total	
Salt-wasting	3 (30%)	31 (69%)	34 (62%)	p value 0.03253*
Simple-virilising	7 (70%)	14 (31%)	21 (38%)	
Total	10 (100%)	45 (100%)	55 (100%)	

In the study population, about 62% were salt wasters and 38% were simple virilisers. The difference is statistically significant as the p value is 0.03253. Distribution among girls was as expected, 69% were salt wasters and 31% were simple virilisers. But among boys, it was opposite, 30% were salt-wasters and 70% were simple-virilisers.



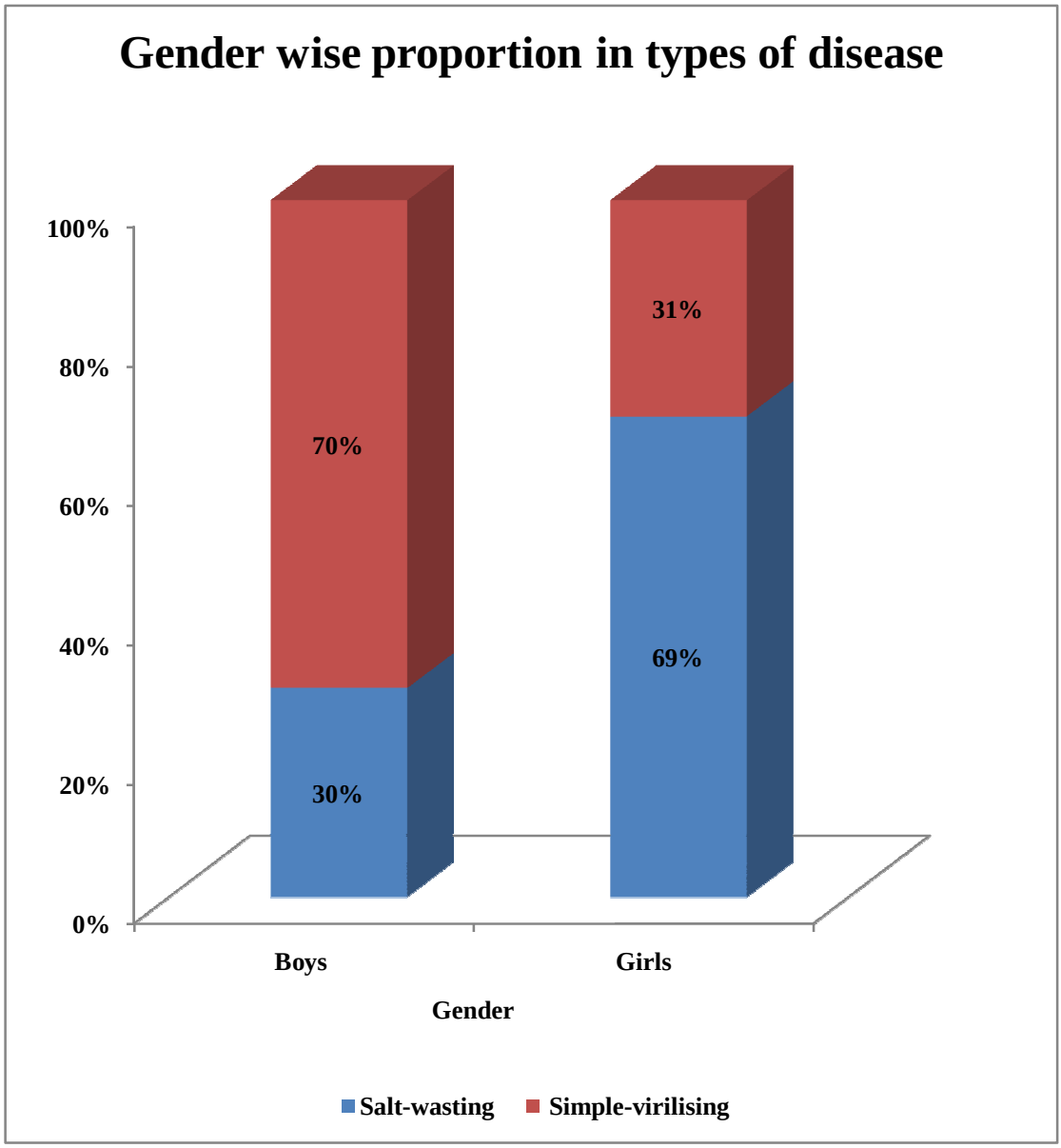

Gender wise proportion in types of disease
100%
80%
60%
40%
20%
0%
70%
30%
31%
69%
Boys
Girls
Gender
Salt-wasting
Simple-virilising

Table 6 : Distribution of dose of steroid used for treatment in this study population

Steroid dose	Type of disease		
	Salt-wasting	Simple-virilising	Total
>20	8 (24%)	6 (29%)	14 (25%)
15-20	14 (41%)	8 (38%)	22 (40%)
10-15	9 (27%)	6 (29%)	15 (27%)
5-10	3 (9%)	1 (5%)	4 (7%)
Total	34 (100%)	21 (100%)	55 (100%)

In our study, about 40% of the total populations were on recommended dose of steroids. 27% of the patients were taking 10 to 15 mg/m^2. 25% of the total populations were taking above the required dose of steroid.

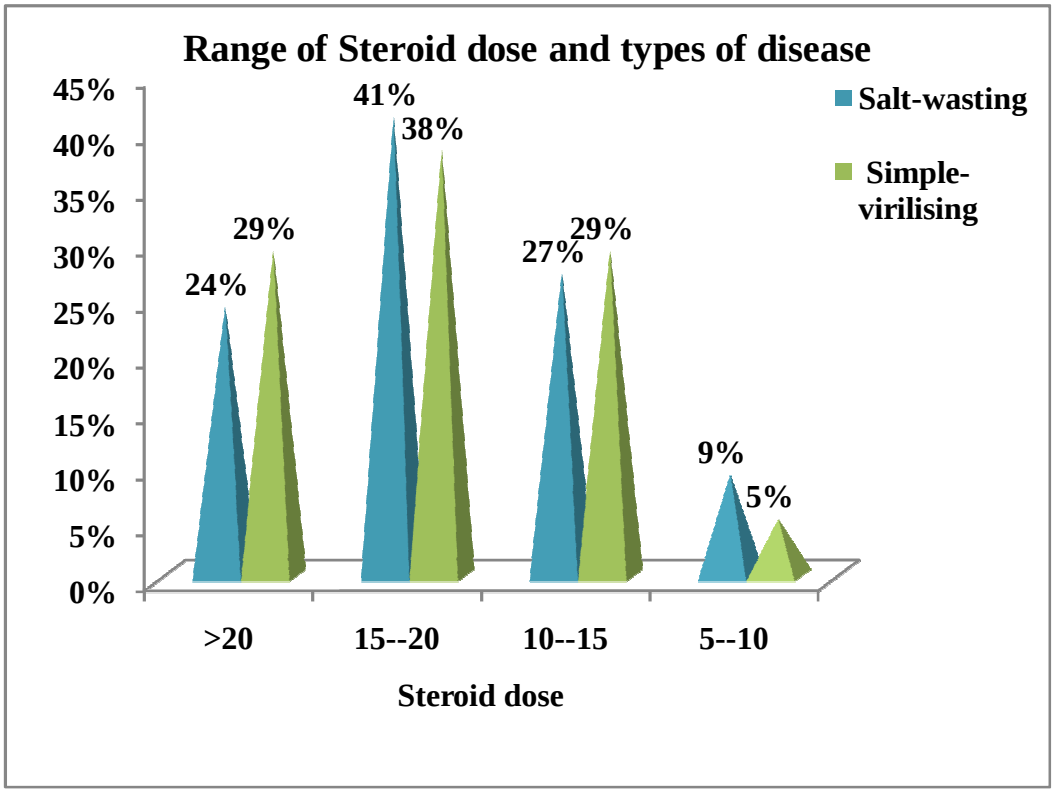


Table 7 : Distribution of Consanguity among the study population

	Types of disease			Fisher's exact test
Consanguity	**Salt-wasting**	**Simple-virilising**	**Total**	
Consanguineous	30 (88%)	17 (81%)	47 (85%)	P value 0.4641
Non-consanguineous	4 (12%)	4 (19%)	8 (15%)	
Total	34 (100%)	21 (100%)	55 (100%)	

86% of the total study population were born of consanguineous marriage. 88% of the salt wasters were born of consanguineous marriage where as 81% of the simple virilisers were born of consanguineous marriage though the difference is not statistically significant.

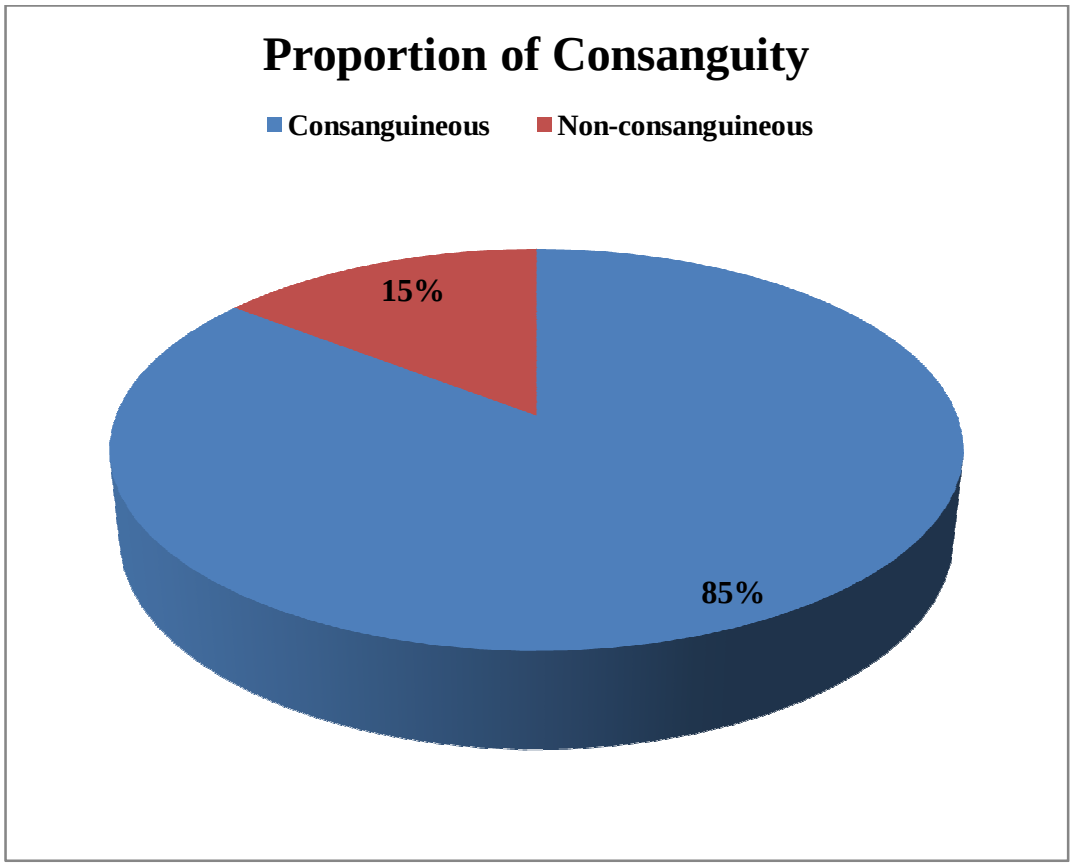
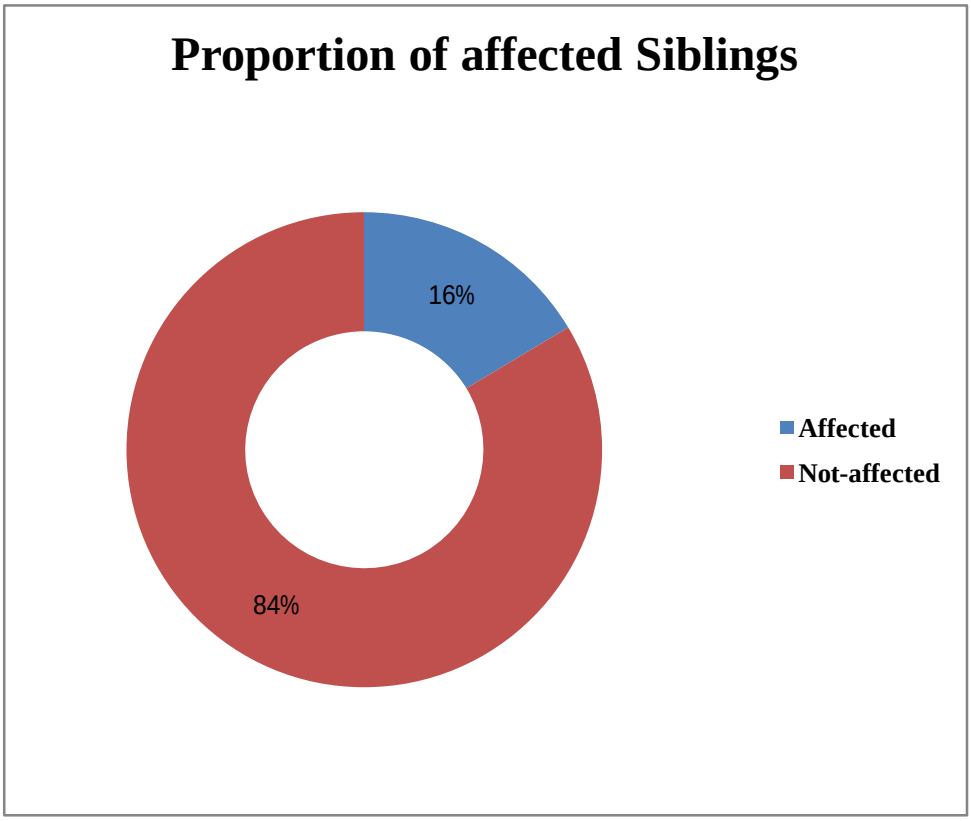


Table 8 : Distribution of positive family history in the study

Siblings	Types of disease			Fisher's Exact Test
	Salt-wasting	Simple-virilising	Total	
Affected	2 (6%)	7 (33%)	9 (16%)	p value 0.0196
Not affected	32 (94%)	14 (67%)	46 (84%)	
Total	34 (100%)	21 (100%)	55 (100%)	

In this study, totally 16% had their siblings affected and the history of Siblings being affected was significantly associated with types of disease at p = 0.0196.



Distribution of affected siblings among the two types of CAH in the study population

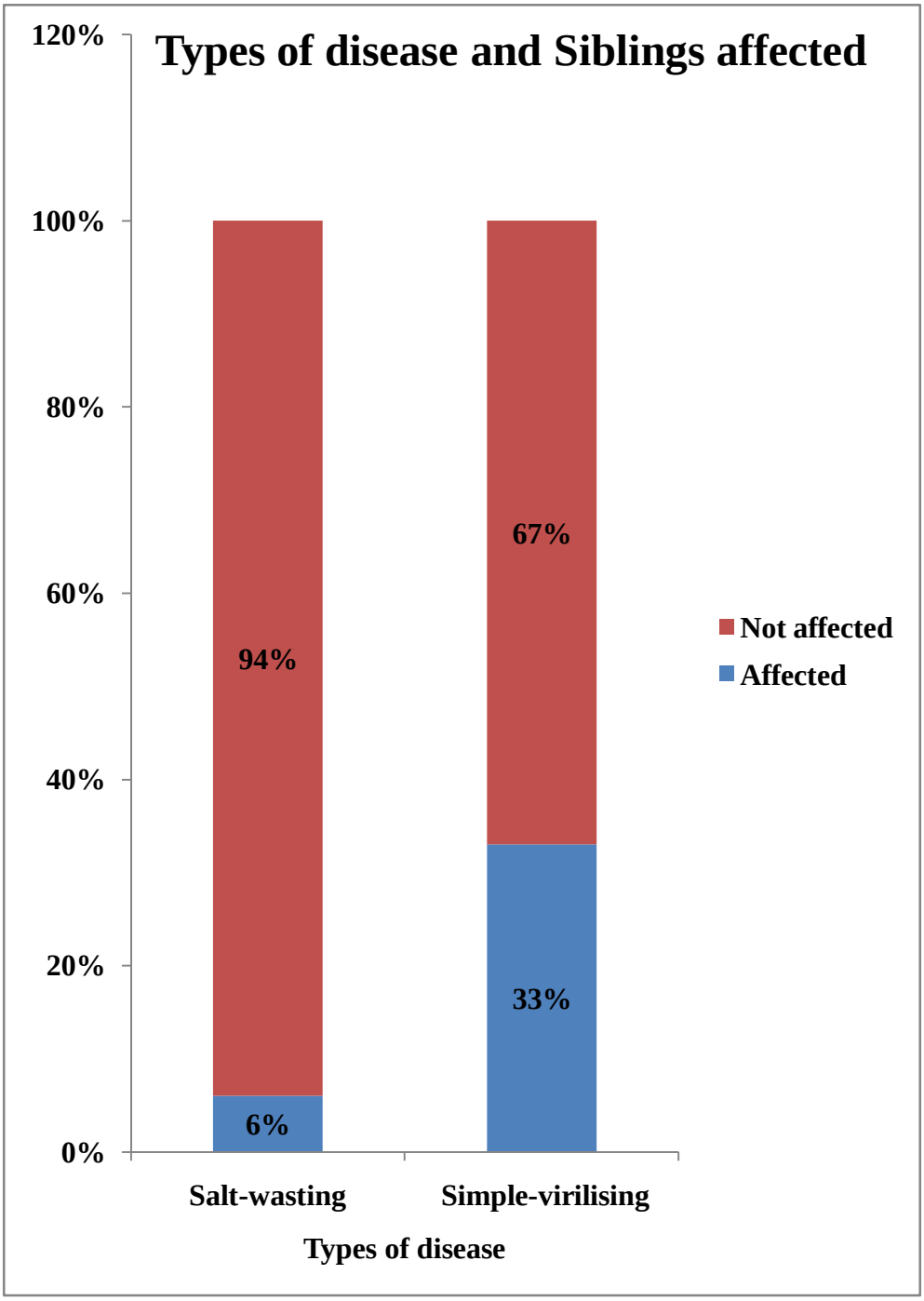


Table-9 Distribution of height z-scores among the study population

Height (Z score)	Types of disease			Fisher's exact test
	Salt-wasting	Simple-virilising	Total	
< -3	2 (6%)	3 (14%)	5 (9%)	p value 0.2658
(-2) - (-3)	4 (12%)	0	4 (7%)	
(2) - (-2)	21 (62%)	16 (76%)	37 (67%)	
2 – 3	3 (9%)	0	3 (6%)	
> 3	4 (12%)	2 (10%)	6 (11%)	
Total	34 (100%)	21 (100%)	55 (100%)	

In this study , 67% of the total population had normal height z-scores. 20% of them had either short stature(9%) or tall for their age(11%). In our study, 76% of simple virilisers had normal height Z score and only 62% of salt waters had normal Height z score but the difference is statistically not significant.

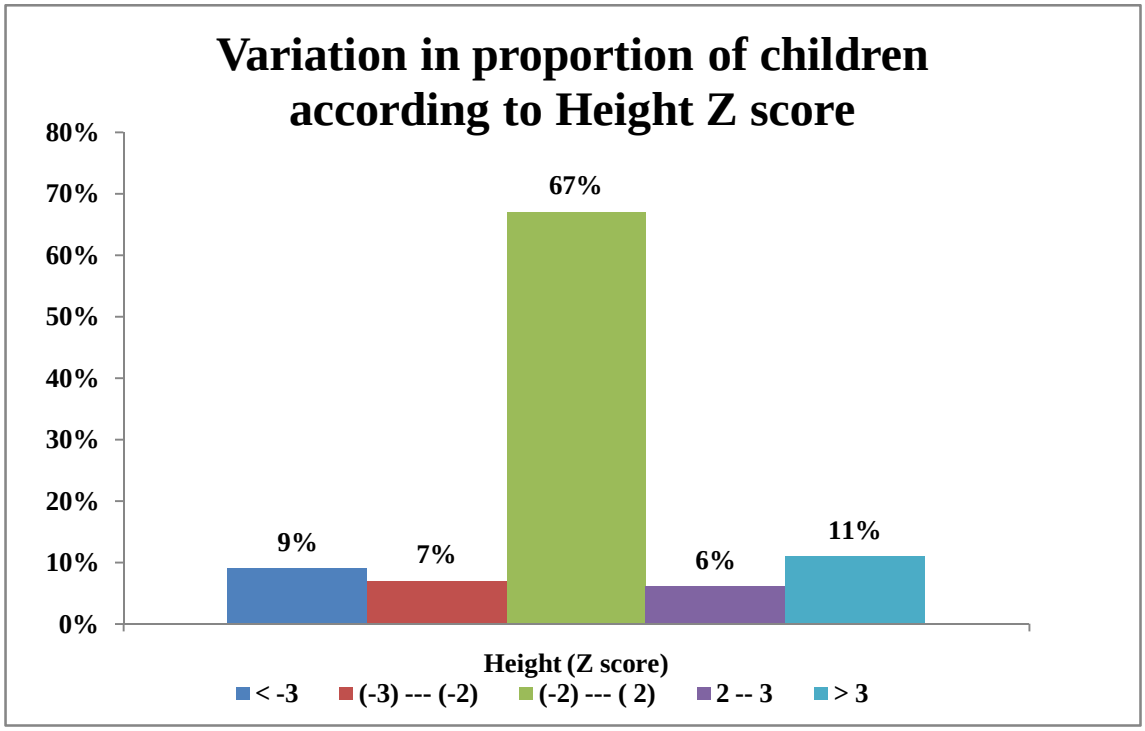


Table-10 Correlation between steroid dose and height

Steroid dose	Height
N	**55**
Pearson Correlation	**-0.357**
P value	**0.007***

Steroid dose and height in our study showed only a poor negative correlation with r= -0.357.

Table-11 Correlation between height and duration of treatment

Height (in Z score)	Duration of treatment
N	55
Pearson Correlation	0.073
P value	0.597

No significant correlation could be established between height and duration of treatment in this study.

Table-12 Distribution of weight z-scores among the study population

Weight (Z score)	Types of disease			Fisher's exact test
	Salt-wasting	Simple-virilising	Total	
< -3	0	3 (14%)	3 (6%)	p value 0.1076
(-2) - (-3)	2 (6%)	1 (5%)	3 (6%)	
(2) - (-2)	26 (77%)	16 (76%)	42 (76%)	
2 – 3	2 (6%)	1 (5%)	3 (6%)	
> 3	4 (12%)	0	4 (7%)	
Total	34 (100%)	21 (100%)	55 (100%)	

In this study , 72% of the kids had their weight z-score normal. 7% of them had fallen under >+3 z-score. Weight (score) was not associated with types of disease at p = 0.1076. The difference was due to chance.

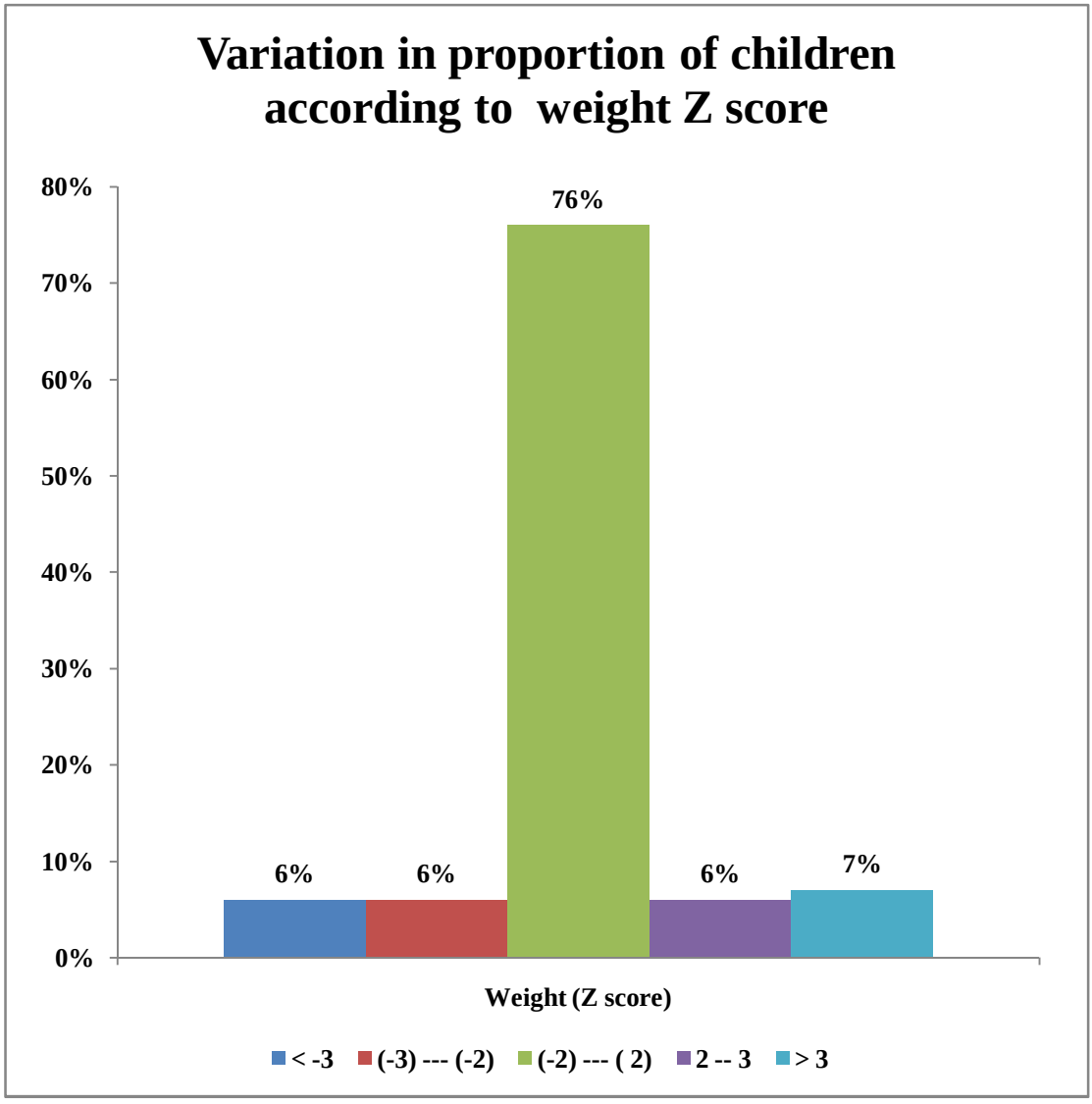


Table-13 Distribution of BMI among the study population

BMI	Types of disease			Fisher's exact test
	Salt-wasting	Simple-virilising	Total	
Obesity	7 (21%)	4 (19%)	11 (20%)	p value 0.7365
Overweight	7 (21%)	3 (14%)	10 (18%)	
Normal	14 (41%)	12 (52%)	26 (47%)	
Underweight	6 (18%)	2 (10%)	8 (15%)	
Total	34 (100%)	21 (100%)	55 (100%)	

In this study , only 47% of them had normal BMI. 20% of them were obese. 18% were overweight. BMI was not associated with types of disease at p = 0.7365. The difference was due to chance.

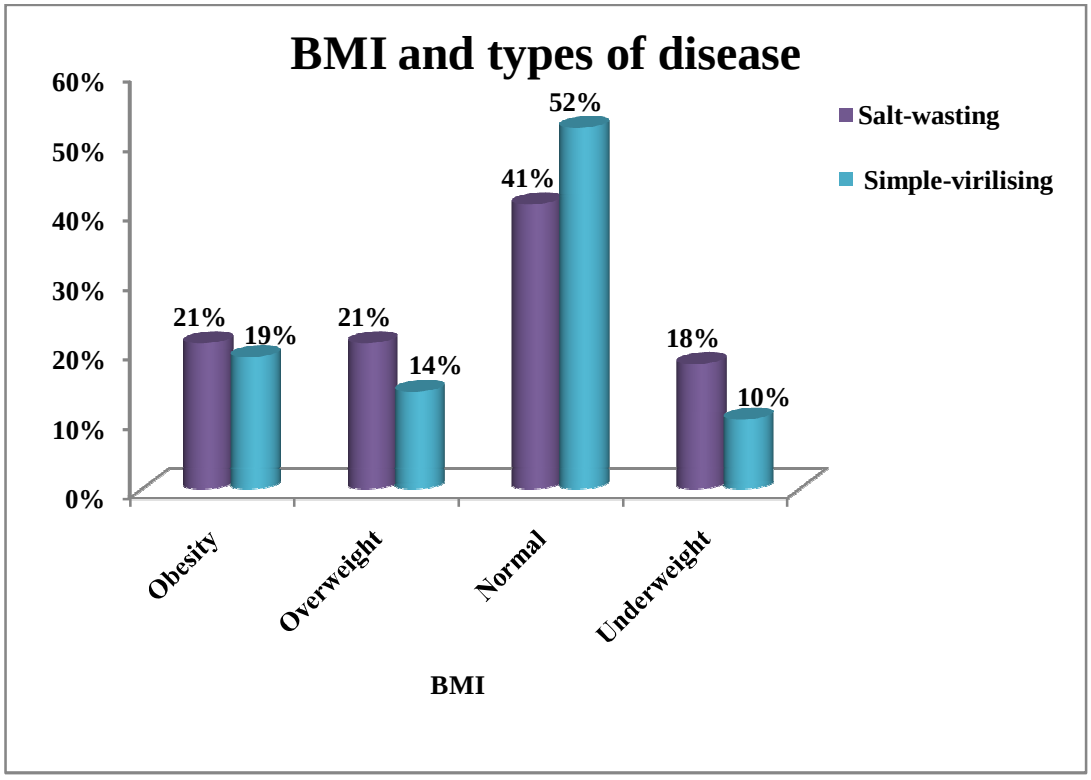


Table-14 Distribution of cushingoid features among the study population

	Types of disease			Fisher's exact test
Steroid excess	**Salt-wasting**	**Simple-virilising**	**Total**	
Present	10 (29%)	5 (24%)	15 (27%)	p value 0.7608
Absent	24 (71%)	16 (76%)	40 (73%)	
Total	34 (100%)	21 (100%)	55 (100%)	

In our study, about 27% of the total kids are found to have features of steroid excess. Cushingoid features are more with salt wasters though the difference is not statistically significant.

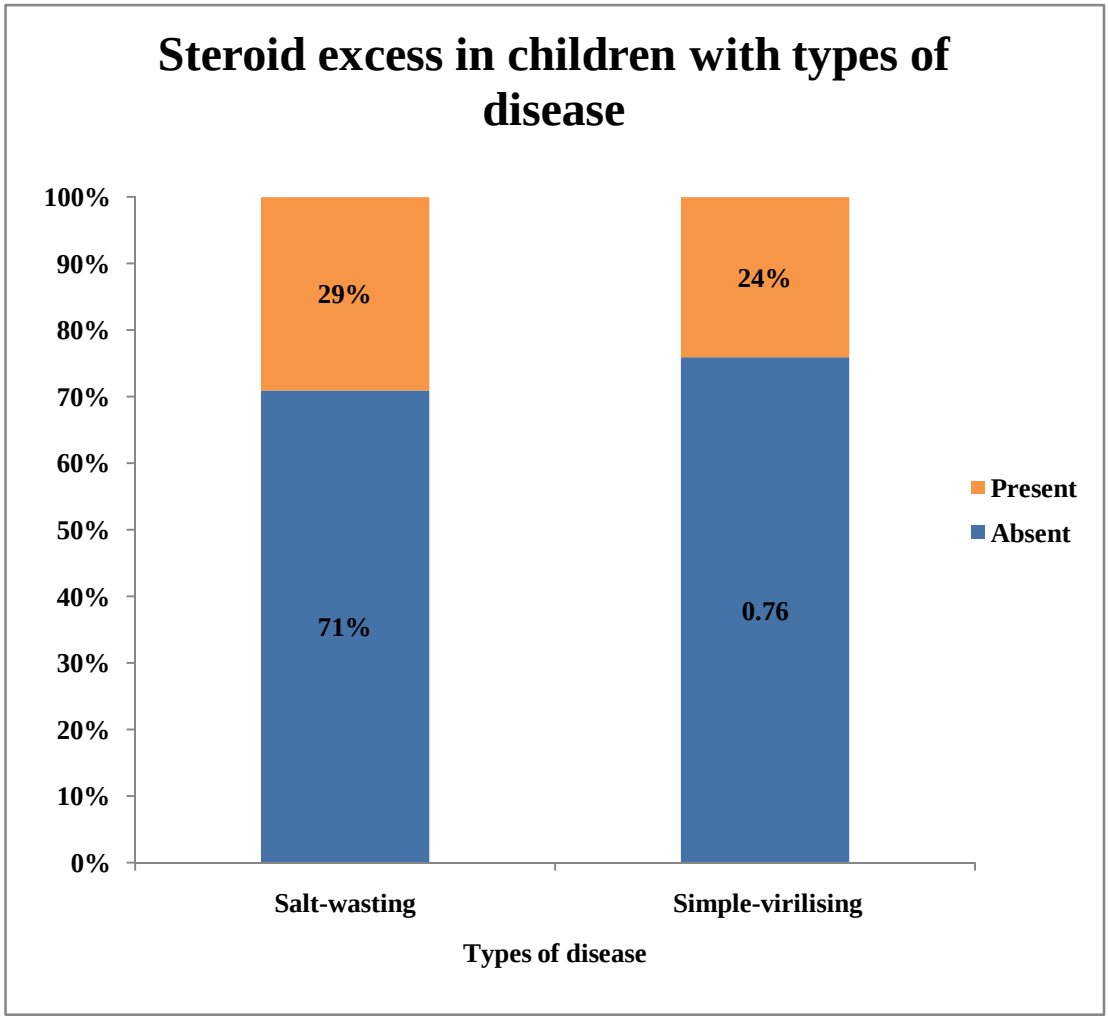


Table-15 Distribution of blood pressure among the study population

Systolic BP	Types of disease			Fisher's exact test
	Salt-wasting	Simple-virilising	Total	
<90	26 (77%)	17 (81%)	43 (78%)	p value 0.7505
90--95	8 (24%)	4 (19%)	12 (22%)	
>95	0	0	0	
Total	34 (100%)	21 (100%)	55 (100%)	

In this study, 78% of them had normal blood pressure. 22% of them had their BP in the pre-hypertensive stage. systolic BP percentiles was not associated with types of disease at p = 0.7505. The difference was due to chance.

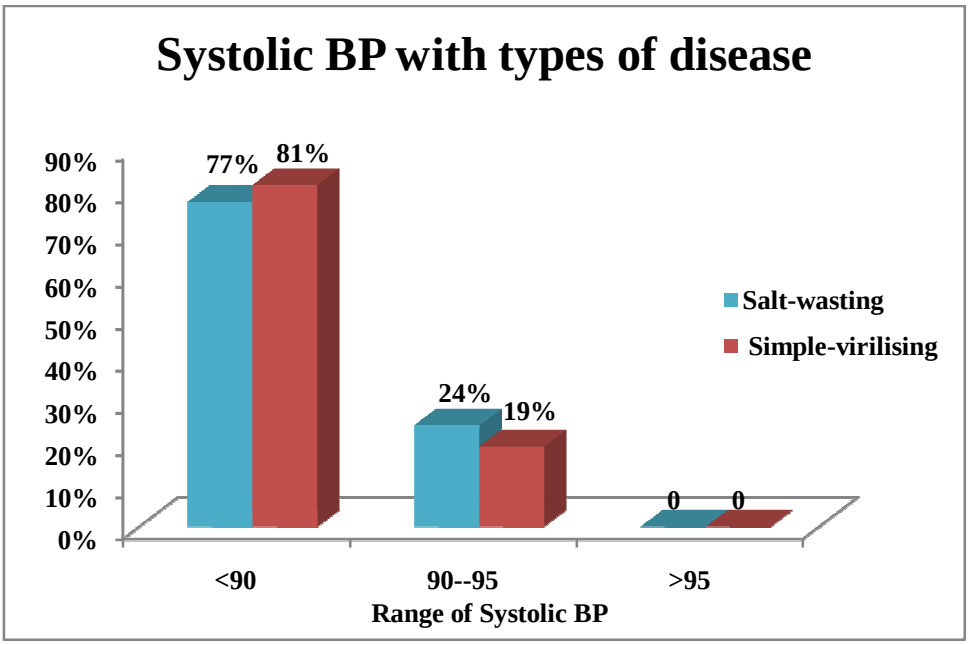
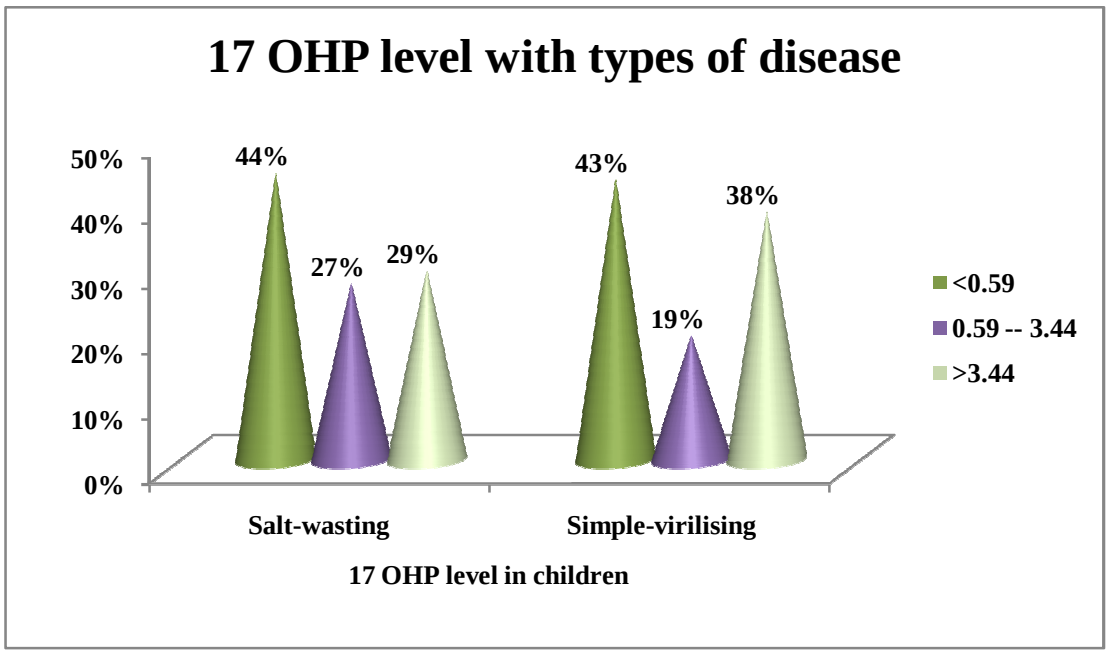


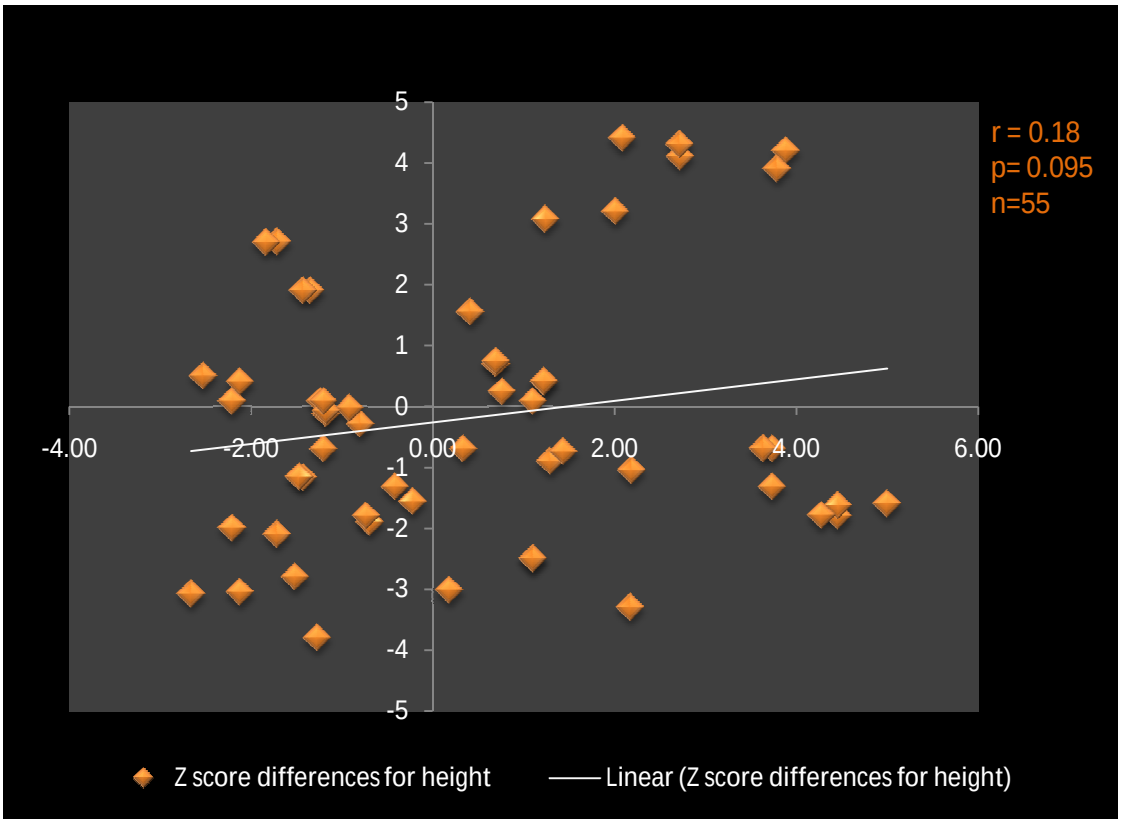
Table-16 Distribution of 17OHP levels among the types of study population

17 OHP	Types of disease			Fisher's exact test
	Salt-wasting	Simple-virilising	Total	
< 0.59	15 (44%)	9 (43%)	24 (44%)	p value 0.729
0.59 -- 3.44	9 (27%)	4 (19%)	13 (24%)	
>3.44	10 (29%)	8 (38%)	18 (33%)	
Total	34 (100%)	21 (100%)	55 (100%)	

In this study , only 24% of them had the expected fair control levels of 17OHP. 44% of them were under tight control. 33% of them had higher levels of the hormone. 17 OHP was not associated with types of disease at p = 0.729. The difference was due to chance.



Correlation between 17-OHP values (natural logarithms) and height z scores of 55 CAH children

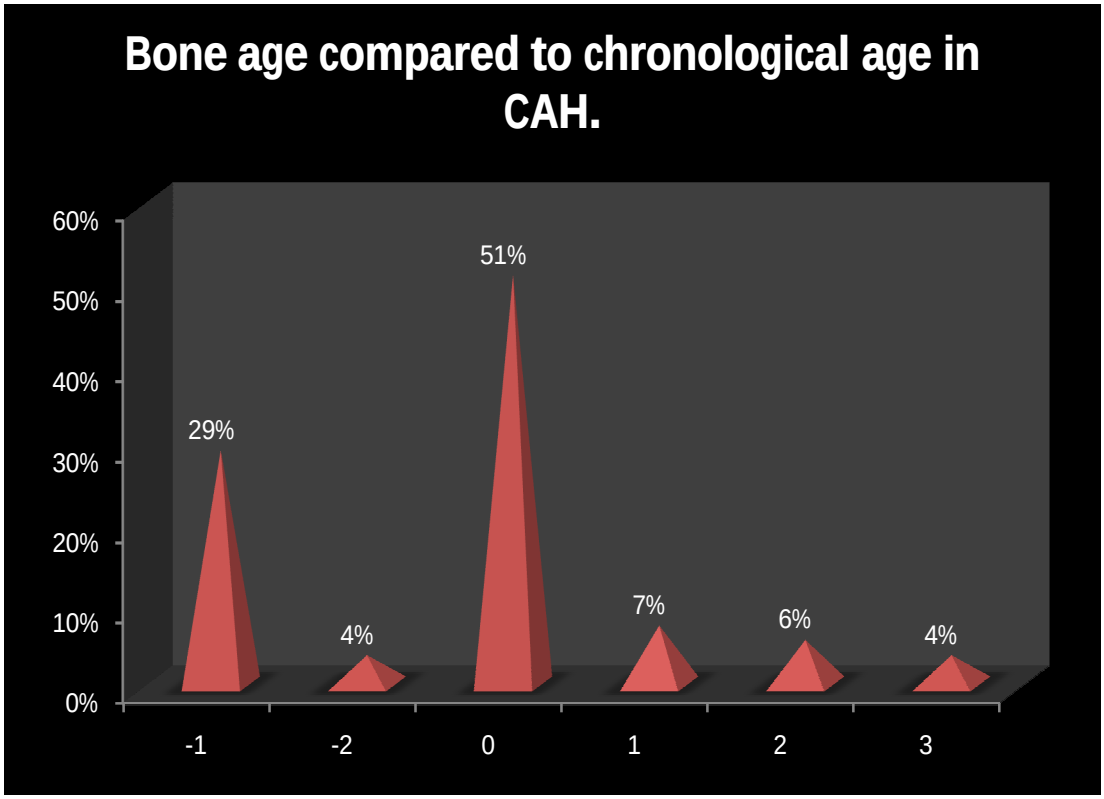


In this study, Correlation studies between 17-OHP values (natural logarithms) and height z scores of 55 CAH children showed weak correlation at r= 0.18, p= 0.95. The sample size (n=55) may not be enough to prove the significance between 17-OHP values (natural logarithms) and height z scores.

Table 17 Distribution of bone age among the study population

Bone Age	Types of disease			Fisher's exact test
	Salt-wasting	Simple-virilising	Total	
-2	1 (3%)	1 (5%)	2(4%)	p value 0.5053
-1	12 (35%)	4 (19%)	16 (29%)	
0	14 (41%)	14 (67%)	28 (51%)	
1	3 (9%)	1 (5%)	4 (7%)	
2	2 (6%)	1 (5%)	3 (6%)	
3	2 (6%)	0	2 (4%)	
Total	34 (100%)	21 (100%)	55 (100%)	

In this study , about 4% of them had advanced bone age by 3 years and 4% of them had delayed bone age by 2 years. Bone age was not associated with types of disease at p = 0.5053. The difference was due to chance.(-2 implies that the bone age is delayed by 2 years and 3 indicates that bone age is advanced by 3 years).


Bone age compared to chronological age in CAH.
60%
50%
40%
30%
20%
10%
0%
29%
4%
51%
7%
6%
4%
-1
-2
0
1
2
3

.

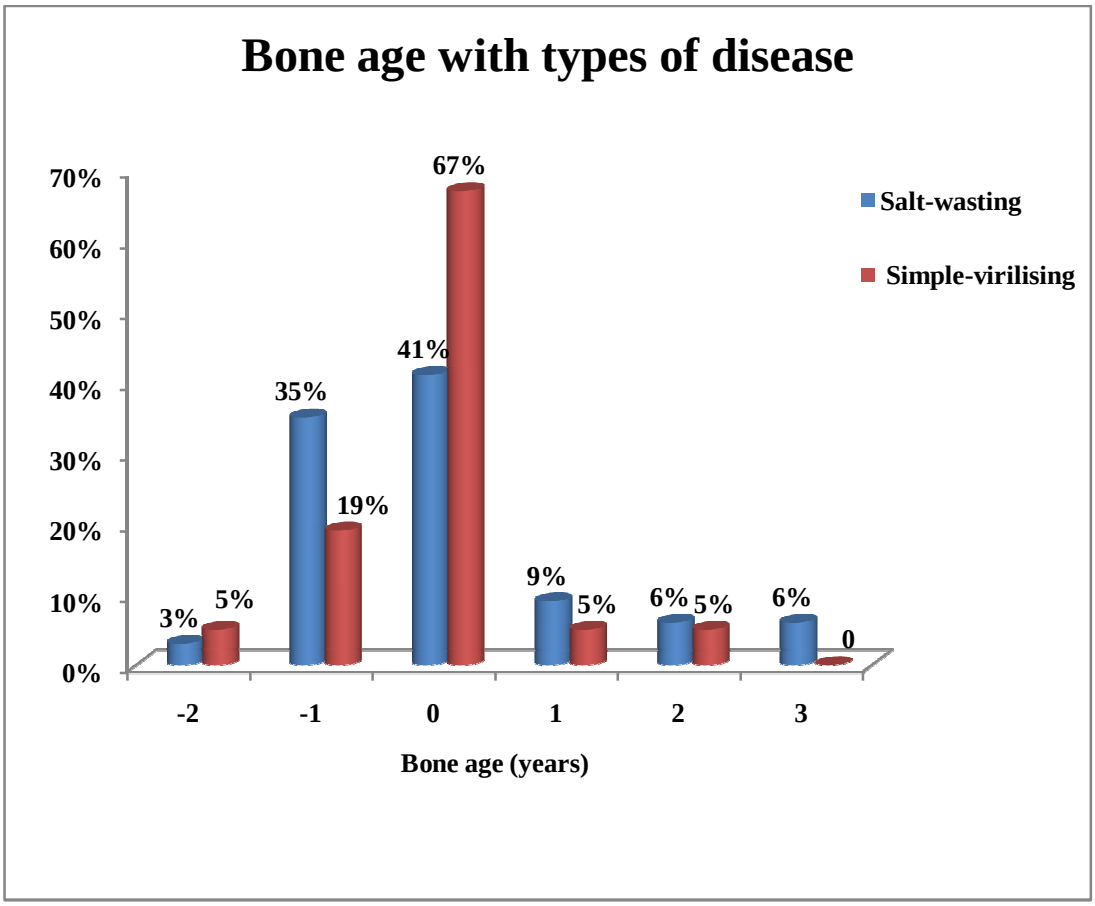

Bone age with types of disease
70%
60%
50%
40%
30%
20%
10%
0%
3%
5%
35%
19%
41%
67%
9%
5%
6%
5%
6%
0
-2
-1
0
1
2
3
Bone age (years)
Salt-wasting
Simple-virilising

Table 18 Distribution of social adaptive behavior among the study population

Social adaptive behavior	Types of disease			Fisher's exact test
	Salt-wasting	Simple-virilising	Total	
Adequate	16 (47%)	13 (62%)	29 (53%)	p value 0.5648
Moderately low	15 (44%)	7 (33%)	22 (40%)	
Low	3 (9%)	1 (5%)	4 (7%)	
Total	34 (100%)	21 (100%)	55 (100%)	

In this study , 53% of the population had adequate adaptability and 40% of them had moderately low adaptability. 7% had low adaptability. social adaptive behavior was not associated with types of disease at p = 0.5648. The difference was due to chance.

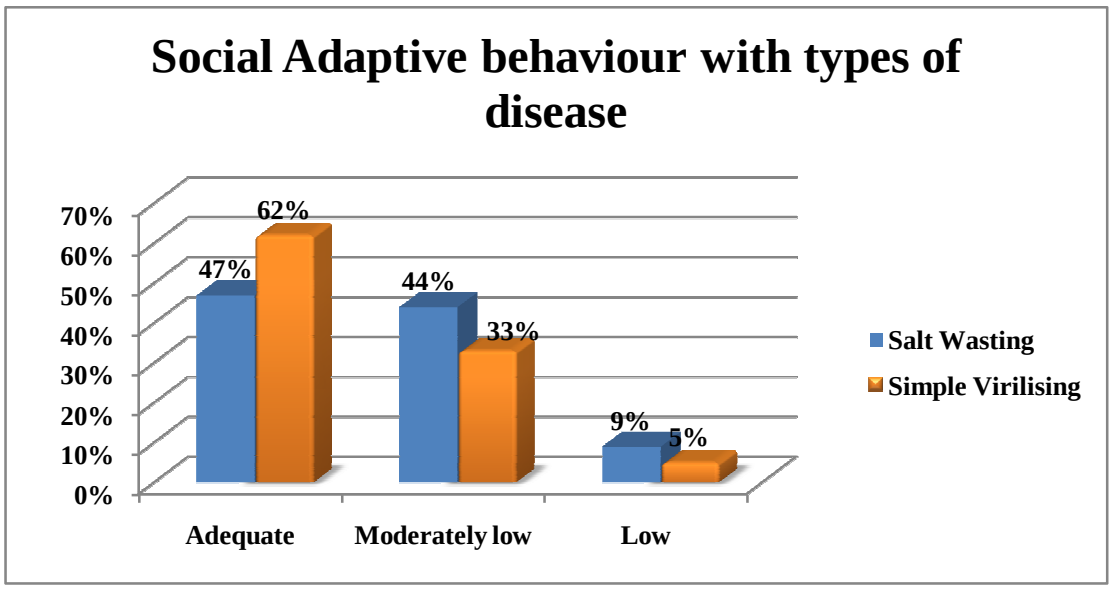


Table 19 Distribution of aggression among the study population

Aggressiveness	Types of disease			Fisher's exact test
	Salt-wasting	Simple-virilising	Total	
Not significant	28 (82%)	16 (76%)	44 (80%)	p value 0.7309
Aggressive	6 (18%)	5 (24%)	11 (20%)	
Total	34 (100%)	21 (100%)	55 (100%)	

In this study, 20% of the total study population were found to be aggressive. Aggressiveness was not associated with types of disease at p = 0.7309. The difference was due to chance.

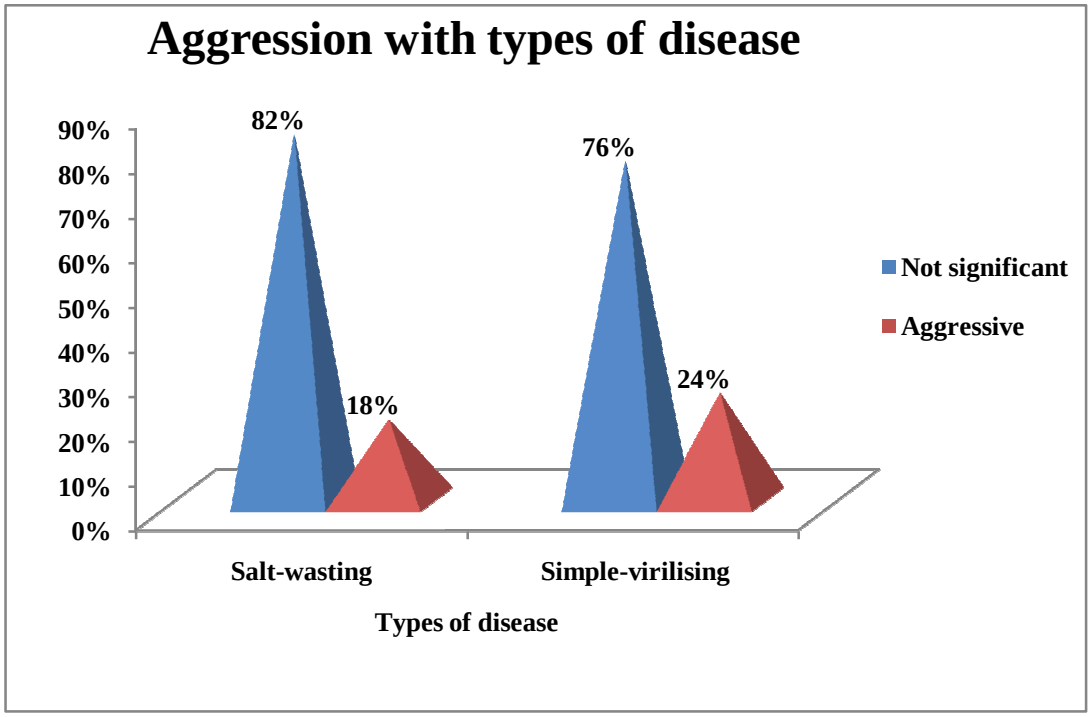


Table 20 Distribution of aggressiveness among two gender in CAH

CBCL	Gender			Fisher's exact test
	Boys	Girls	Total	
Not significant	8 (80%)	36(80%)	44 (80%)	p value 1.000
Aggressive	2 (20%)	9 (20%)	11 20%)	
Total	10 (100%)	45 (100%)	55 (100%)	

There was no statistical significant association between aggressiveness and Gender at p = 1.000. That is, aggressiveness and gender were not dependent to each other in CAH.

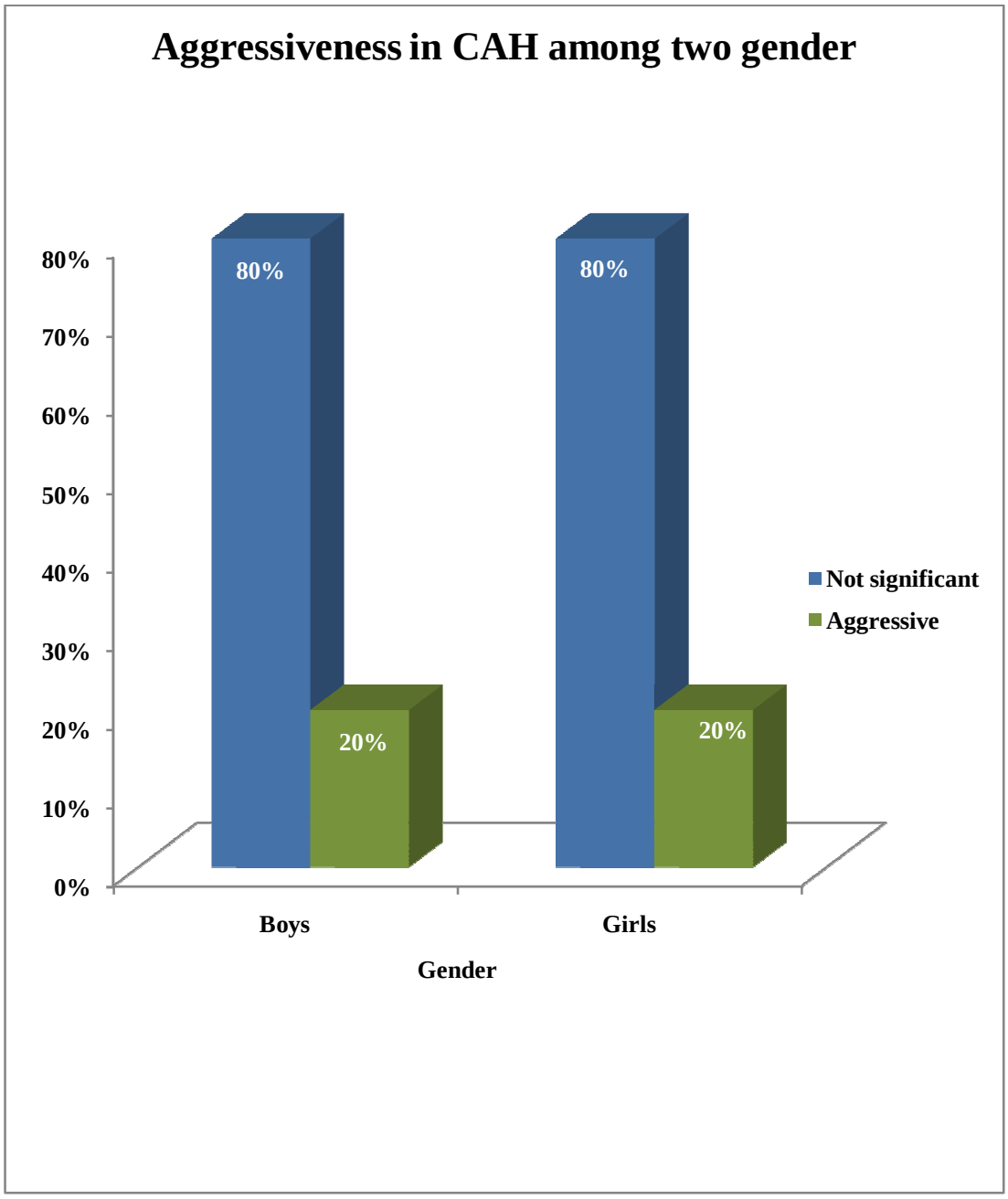


Table 22 Prediction of aggressiveness:

Variables	B	S.E.	p value	Exp(B)
Steroid dose	0.232	0.093	**0.012***	1.261
Duration of treatment	0.010	0.009	0.279	1.01
17 OHP	0.009	0.012	0.45	1.009
Constant	-6.374	2.006	0.001	0.002

In this study, Steroid dose played a significant role to predict the aggressiveness from CBCL at p=0.012. Coefficient of regression B =0.232 shows a good predictor of aggressiveness from CBCL. Steroid dose increase the odds by 1.261. Duration of treatment & 17 OHP not increase or decrease the odds since E(B) = 1.01 & 1.009 respectively were approximately to 1.

Hence, finally concluded from my study, based on the above said results, that from the steroid dose we could predict aggressiveness whereas from duration of treatment or from 17OHP levels, we could not predict.

Table 23 Distribution of ADHD among the study population

ADHD	Types of disease			Fisher's exact test
	Salt-wasting	Simple-virilising	Total	
No ADHD	28 (82%)	19 (91%)	47 (86%)	p value 0.696
ADHD	6 (18%)	2 (9%)	8 (15%)	
Total	34 (100%)	21 (100%)	55 (100%)	

In this study , 15% of the total population had ADHD. ADHD was not associated with types of disease at p = 0.696. The difference was due to chance.

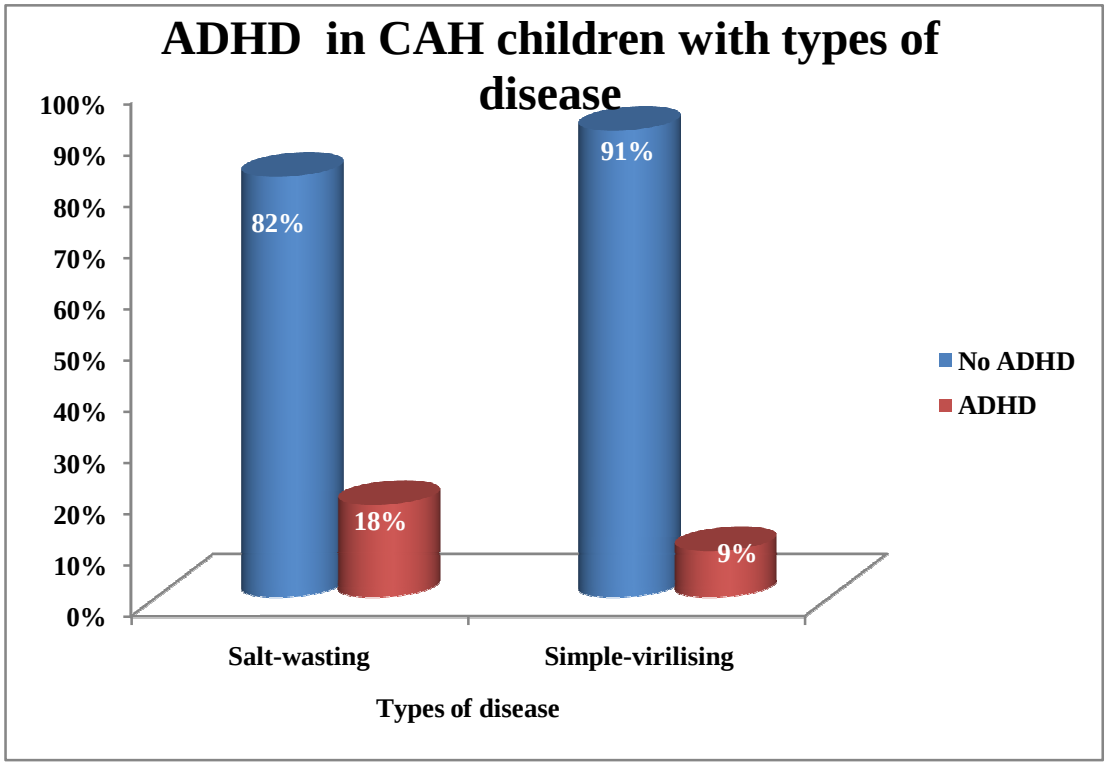


Table 24 Sex distribution of ADHD among the study population

ADHD	Gender			Fisher's exact test
	Boys	**Girls**	**Total**	
No ADHD	9 (90%)	38 (84%)	47 (85%)	p value 1.000
ADHD	1 (10%)	7 (16%)	8 (15%)	
Total	10 (100%)	45 (100%)	55 (100%)	

In our study, 16% of the girls and only 10% of the boys had ADHD. But the difference is not statistically significant as the p value is 1.000.

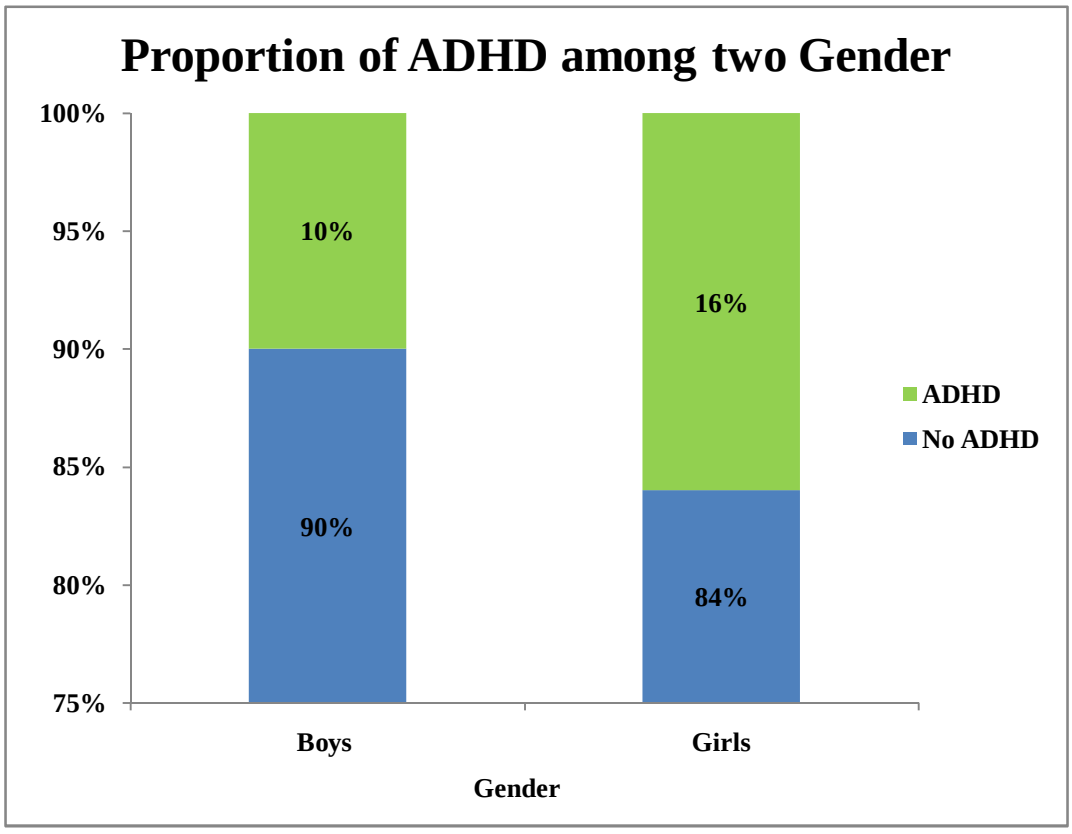


Table 25 Distribution of IQ among the two types of CAH in the study population

IQ range	Types of disease			Fisher's exact test
	Salt-wasting	Simple-virilising	Total	
50-70	1 (3%)	1 (5%)	2 (4%)	p value 0.5473
70-90	20 (59%)	9 (43%)	29(53%)	
90-110	13 (38%)	11 (52%)	24 (43%)	
Total	34 (100%)	21 (100%)	55 (100%)	

In this study, 53% of the total population had only borderline IQ levels. IQ range was not associated with types of disease at p = 0.5473. The difference was due to chance.

Distribution of IQ among the study population

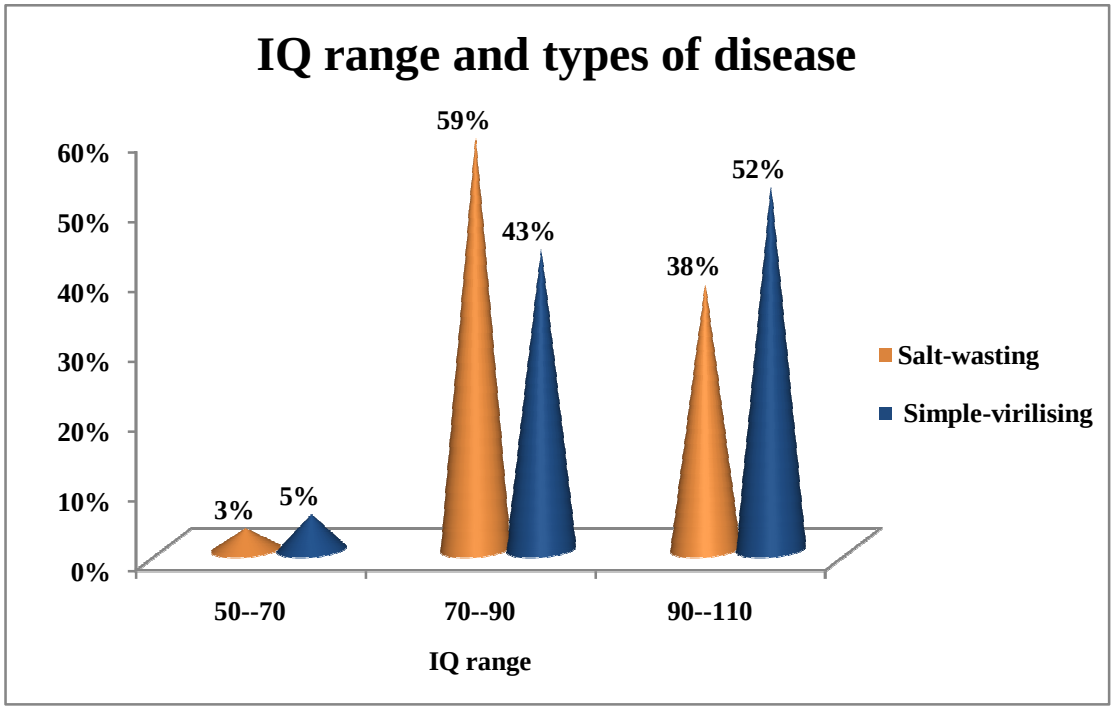


Table 26 Distribution of IQ based on gender

IQ range	Gender			Fisher's exact test
	Boys	Girls	Total	
50-70	1 (10%)	1 (2%)	2 (4%)	p value 0.4375
70-90	5 (50%)	24(54%)	29 (53%)	
90-110	4 (40%)	20 (44%)	24 (44%)	
Total	10 (100%)	45 (100%)	55 (100%)	

IQ distribution pattern among the two sex is not much different from the total with a p value of 0.4375 and hence not statistically significant.

Distribution of IQ among boys and girls

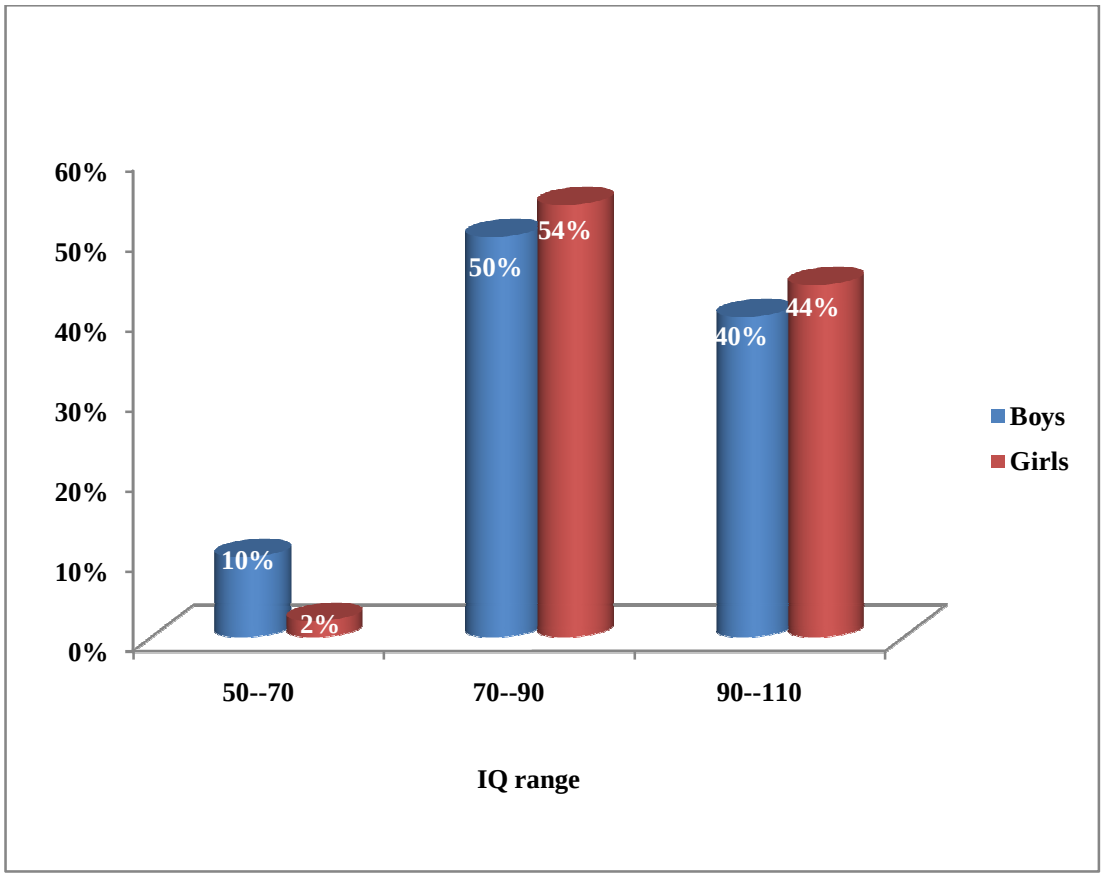


Table 27 Correlation between steroid dose and cushingoid features, 17OHP, adaptive behavior and IQ.

Steroid dose	Cushingoid Features	17 OHP	Adaptive behavior	IQ
N	55	55	55	55
Pearson Correlation	**0.502**	-0.193	0.026	0.055

Steroid dose correlated positively with cushngoid features with r=0.502, whereas it doesnot show any correlation with 17OHP, adaptive behavior and IQ in our study.

DISCUSSION

This study is conducted at endocrinology department of Institute of child health and hospital for children between the period of February 2015 to august 2015. We studied the demographic characteristics, physical, social and cognitive functioning in CAH children. CAH is the most common cause of hyperandrogenism in children. Incidence of the disease is as high as 1 in 15,000.

Totally 55 children between 2 to 12 years of age who met the inclusion and exclusion criteria were enrolled into the study. Among them, 82%(n=45) were females and only 18% (n=10)were males. Though the incidence of the disease does not have any significant sex difference, it has been shown that CAH in males have been under diagnosed in our population. There had been studies stating that incidence of the disease is more in boys than girls between 0 to 12 years[88]. The reason for discrepancy in our study may be due to:

1. Male children may go undiagnosed in simple virilising type.
2. Males with salt wasting type may die undiagnosed. The main cause for this is the absence of newborn screening programs for CAH in India.

Age distribution among the study population has shown us that about 40% of the total study population were between 8 to 12 years. About 30% of the total study population were between 2 to 4 years. Remaining 30% were

between 5 to 7 years. Age and sex distribution doesnot show any significance in our study.

Median age of diagnosis in our study is less than 1 month, though the range may be from 1 month to 72 months. Similarly in a study done by Ivani Novato silva et al[89] the range of age at diagnosis was between 0 to 79 months with a median age of 2.9 months. The reason for this wide range in age at diagnosis, is mainly the difference in cultural practices leading on to ignorance among parents. Interview with these parents have shown us the hesitancy in bringing their kids to the notice of physician. In our study, proportion of girls being diagnosed in the neonatal period is more, upto 89%(n=40) than boys(60%). On the whole about 84% of the kids were diagnosed at the neonatal period in our study. Most of them were diagnosed with salt wasting crisis. This is again due to the absence of newborn screening programs. But still range of age at initial diagnosis is wide in our population compared to many other studies. Male children may have advanced bone age as the only sign and hence it is diagnosed very late or else left undiagnosed.

Comparision between the two types of disease with respect to the age at diagnosis, doesnot show statistical significance.

Two types of disease based on severity classified were salt wasting type which is most severe and the simple virilising type. The most common type is salt wasting which may account for about 70% of the total cases and the remaining 30% are the simple virilising type. In our study, as expected salt wasting type constituted the majority about 62% (n=34). Simple virilizing type

was only 38%(n=21). Considering the difference in sex among these types, females have clearly shown a expected division of 70%(n=31) being salt wasters and 30%(n=14) being simple virilisers. Among males it was the reverse in our study. About 70%(n=7) were simple virilisers and the remaining 30%(n=3) were salt wasters. The difference was statistically significant. ($p<0.05$). In the study done by Sven. C.Muller [87], it has been shown that even among the male population, prevalence of salt wasting type is about 70% .

Sarita et al in her study clearly stated that boys were more diagnosed[88] as salt-wasters compared to girls(boys- 80% were salt wasters and only 50% girls were salt wasters).The cause for this discrepancy in our study may be due to the early death of salt waster males before being diagnosed to have the disease. Hence it is very clear that early diagnosis and treatment is essential for the prevention of mortality in our patients. This again explains the role of newborn screening programs.

Mean dose of steroid administered to our patients in my study is 16.3$\pm$ 4.4 mg/m^2 body surface area. Among females it is 16.3$\pm$4.56 mg/ m^2 and among males it is 15.5$\pm$3.8 mg/m^2. Hence dose requirement among females may be higher and this may be because of the reason that more salt wasters in our study are females. The recommended dose is 15 to 20 mg/m^2. Few articles have quoted that the dose required should be maintained at a very low levels ranging from 10 to 15 mg/m^2[56]. The physiological production of steroids in our body is only in the rate of 4 to 8.7 mg/m^2. Hence in our study about 75% of the total kids receive within or less than this recommended range while the

remaining 25% of the kids receive slightly higher dose than recommended. The reason is due to the poor compliance, hyperandrogenic state may not be controlled with the so called physiological dose and hence the requirement may go high in some. Other cause is the failure to decrease the dose after stepping up during stress period. Poor follow up by some of these patients is yet another cause.

Among the 75% of these patients, few of them(7%) take only 5 to 10 mg/m^2. This group of children either may have good control with this small amount of drug or may not be under strict follow up(in our study two kids who were reported to take this amount of drug were found to have a very high 17OHP levels and not under good control). Hence we can conclude that 50% of these kids who were with low dose than recommended can still have normal control when they were followed up stringently with both clinical assessment and laboratory analysis.

Considering the type of disease and steroid dose, it has been shown that in both these groups majority of them(40%) were on recommended dose. About 30%(n=6) of the simple virilisers were found to take more than the recommended dose. These differences were not statistically significant.

CAH has a autosomal recessive inheritance pattern. Hence history regarding consanguity were taken in to account. In our study it has been shown that 85%(n=47) of kids were born of consanguineous marriage and remaining 15%(n=8) alone were born of non-consanguineous marriage.

About 88%(n=30) of the salt wasters and 81%(n=17) of simple virilisers were born of consanguineous marriage. Though the difference is not statistically significant, from our study it appears that majority of salt wasters were born of consanguineous marriage.

Considering sibling history, we had 4 pairs of siblings being affected and all the 8 were enrolled in to the study. One kid has lost her sister due to salt wasting crisis. Hence totally 16%(n=9) of these kids had a positive sibling history. The difference according to the two types of disease was statistically significant ($p< 0.05$). This had clearly shown the lack of knowledge about the prenatal diagnosis and treatment for congenital adrenal hyperplasia in some areas. Dexamethasone treatment should have been given to the mothers immediately after confirming pregnancy. If these kids were diagnosed early and started on treatment early, even from the antenatal period, outcome would have been better.

Anthropometric measurements which are included in our study are height, weight and body mass index. These measurements are plotted on standard charts. CAH is a disease which is well known to cause alteration in growth patterns, which may be due to both disease process and treatment of the same. Hence it is vital to measure height at regular intervals. In our study, influence of type of disease, dose of steroid and various other factors on height were studied. Mean height z score in our study was -0.2 ± 2.1. In our study, about 67%(n=37) of the total population had their height z- scores between -2 to +2. About 11%(n=6) of them were >+3 z-score and 9%(n=5) of them were

<-3 z-score. Among the patients with height z-scores >+3 z-score, 5 patients were on recommended dose and only one of them were on low dose. But, all 6 of them had 17OHP values above normal range. Hence, this suggests that the requirement of steroids in these patients for control of hyperandrogenic state is higher. Out of the five patients with height z-scores <-3, only two of them were taking more than recommended dose of steroids. Three of them had their 17OHP values less than the normal range. Hence in these patients the steroid dose should be slowly decreased.

Considering the type of disease, among the salt wasters, 62%(n=21) were between -2 to+2 z-score. Among the simple virilisers, 76%(n=16) were between -2 to+2 z score. The difference is not statistically significant. About 7% of our patients were on inadequate steroid dose. Inadequate steroid dose would result in hyperandrogenism and hence would increase the height percentiles. In our study, out of the four kids who were on inadequate dose, two of them had their height z-score more than +3. It has also been proved in one study[89] that children treated with 15 mg/m^2 had better growth velocity than children treated with a dose of 25 mg/m^2. Hence proper growth monitoring and change in steroid dose accordingly is essential. If not monitored, they may land up as dwarf adults. The reason for loss of final height in most of them is quoted as the initial loss of linear growth during the first 2 years of life due to the hypercortisolism in this period[60].

Mean weight z score in our population was 0.2$\pm$1.7. CAH, being treated with steroids, are more prone for obesity. 76%(n=42) of our total population

had their weight z scores between -2 to+2 . Only about 7%(n=4) of kids had their z-scores more than +3. Among the two types of disease, none of the salt wastes were <-3 z-score and none of the simple virilisers were >+3 z-score. The difference is not statistically significant, owing to the small sample size.

BMI status of these patients were thus studied which showed that about 47%(n=26) of our patients had normal BMI. 20%(n=11) of them were obese while 18%(n=10) of them were overweight. Among the 11 obese patients, eight of them were on excess dose of steroids. Hence, regular monitoring of BMI is essential for all CAH patients. Among the types, 52%(n=12) of simple virisers had normal BMI, whereas only 41%(n=14) of the salt wasters only had normal BMI. The difference is not statistically significant. But, In some studies[60] it has been clearly shown that simple virilisers have significantly increased BMI than reference values.

Blood pressure measurements have shown that 78%(n=43) had their systolic blood pressure falling below 90^{th} percentile. About 22%(n=12) had their BP falling in the pre-hypertensive range(90-95^{th} percentile). Among these 12 patients about 67% (n=8) of them were on excess dose of steroids. Hence regular monitoring of BP is essential for patients who are on excess steroid doses. Differentiating between the two groups, 77%(n=26) of the salt wasters and 81%(n=17) of the simple virilisers had their BP < 90^{th} percentile though not statistically significant.

We have also studied for the features of steroid excess in our population. In our study about 27%(n=15) of the total population had cushingoid features.

Among salt wasters about 29%(n=10) and among simple virilisers, about 24%(n=5) had features of steroid excess. This difference was not statistically significant.

17OHP levels were compared between the two groups. Levels between 0.59 and 3.44 ng/ml were taken as normal from the laboratory reference values. From the results obtained, only about 24%(n=13) of the total study population had their 17OHP levels within their normal limits. 44%(n=24) of the patients had their levels below 0.59 ng/ml and hence could considered to have very tight control with steroids. The disadvantage is that they may land up finally with features of steroid excess, though some patients may need such high levels for adequate control of hyperandrogenic state. 33%(n=18) had their 17OHP levels more than 3.44 ng/ml showing their hyperandrogenic state. Since 17OHP levels were directly related to the androgenic state and hence the height, correlation graph was plotted between the height z-score and 17OHP levels which was not statistically significant because of the small sample size.

Bone age measurements were done using x-rays in our study. It is compared with the chronological age and found that 51%(n=28) of the total population had bone age corresponding their chronological age. 4%(n=2) of them had their bone age advanced by 3 years and 4%(n=2) had delayed bone age. Comparing between the two types of disease, 67%(n=14) of the simple virilisers and 41% (n=14) of the salt wasters had normal bone age. None of the simple virilisers had their bone age advanced by 3 years but 6%(n=2) of salt wasters had the same. Though not statistically significant it could be considered

from our study that salt wasters may may have poor control over their bone age than simple virilisers.

Social adaptive behavior of these children was studied using vineland adaptive behavior scale. 53%(n=29) of the kids had adequate adaptive behavior. 40%(n=22) of the kids had moderately low adaptive behavior. Among these 22 kids, seven kids had been on excess steroid dose than recommended and 17OHP levels seen among these 22 showed eight of them with high levels and eight had less than normal range. Hence it could be concluded that both hypercortisolism and hyperandrogenism may decrease the adaptability. 7%(n=4) of the kids had low adaptive levels. Among these 4 kids, one kid had been on excess steroid dose than recommended and two of them had 17OHP levels less than normal range. Comparing the two varieties of disease, simple virilisers have better adaptive levels than salt wasters, though not statistically significant.

Aggressiveness is one of the feature associated with hyperandrogenic state. Many studies have proved that girls with CAH are more aggressive than unaffected girls[76]. They have also stated that girls and boys with CAH do not differ much in aggressiveness. In our study, 20%(n=11) of the affected kids were aggressive. Among the general population between 2 to 17 years, the prevalence of aggression is 2% to 16%. Among males it is 6% to16% and among females it is 2% to 9%. Our study has shown a higher proportion of patients with aggressiveness than in the general population. In our study, aggressiveness is screened from child behavior check checklist (CBCL).

Between the types of disease, 24%(n=5) of the simple virilisers and 18%(n=6) of the salt-wasters were aggressive. The difference is not statistically significant. Considering sex difference, both boys and girls are equally affected. This is against the study done by Vickie Pasterski et al [76], which has stated that aggression is less among CAH boys compare to CAH girls. Based on the analysis, prediction of aggressiveness from the dose of steroid could be done at a p value of 0.012.

Incidence of ADHD among general population is 5 to 12 %. In our study about 15%(n=8) of our population were found to have ADHD based on CBCL. Studies have shown higher incidence of psychiatric disorders like ADHD and autism among these children[87]. Among the two disease types salt wasters(18%,n=6) were found to be more affected than simple virilisers(15%,n=2). Comparing between boys and girls, in our study girls(16%,n=7) were found to be more affected than boys(10%,n=1) though not statistically significant.

Mean full scale IQ in our study is 84.6$\pm$9.8, but in one study[80], it was found to be 84.5. Among the total population about 43%(n=24) of them had normal IQ scores. About 53%(n=29) of the patients were in the borderline level. In our study, Salt wasters were more affected than simple virilisers, though not statistically significant. It has been stated in other studies also that salt wasters have lower IQ scores than simple virilisers[80]. Between the two sex, not much of difference were noted. 4%(n=2) of the total population had IQ scores between 50 to 70. Both were on excess steroid dose(>20 mg/m^2) .Their

17OHP levels were also uniformly very low. Among the 29 patients with borderline impairment, about 41%(n=12) of them had very low 17OHP levels. Hence based on all these factors, the dose should be adjusted adequately to maintain the needed control over the hyperandrogenic state.

CONCLUSION:

- 20% of our CAH population had altered growth pattern and hence frequent monitoring of Height, weight and BMI is essential for all patients with CAH, irrespective of the type of disease, for better outcomes.
- 22% of our CAH population are in the pre-hypertensive stage and majority of them were on excess dose of steroid and hence adequate modification of steroid dose based on clinical findings and hormonal assays should be done.
- Treatment goal should not be set as full suppression of 17 0HP but should be set at normal growth pattern with no features of steroid excess.
- In our study, 53% of the CAH patients had only border line IQ levels. 47% had low social adaptability. 20% had aggression and 15% had ADHD. Hence, all CAH patients should be subjected to psychological and cognitive assessment routinely.

LIMITATIONS

1. Growth velocity should be ideally measured rather than height.
2. Other hormonal assays like androstenedione should have been additionally measured for appropriate determination of hyperandrogenic state.
3. Small sample size.

RECOMMENDATIONS

1. Newborn screening for CAH should be implemented in our country to prevent the mortality and morbidity due to the disease.
2. Study based on growth velocity should be ideally done in our population.
3. Multicentric study should be done with a large sample size.
4. Importance of Early Psychological Assessment should be conveyed to all treating physicians.

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ABBREVATIONS

CAH	-	Congenital adrenal hyperplasia
ACTH	-	Adreno cortico tropic hormone
17OHP	-	17-hydroxy progesterone
CRH	-	Corticotrophin releasing hormone
DOC	-	Deoxycortisol
DOCA	-	Deoxycorticosterone acetate
AVP	-	Arginine vasopressin
BKT	-	Binet kamath test
MISIC	-	Malins intelligence scale for Indian children
IGF-1	-	Insulin like growth factor-1
IGF BP	-	Insulin like growth factor binding protein
FH	-	Final height
TH	-	Target height
SW	-	Salt Wasters
SV	-	Simple Virilizers
ADHD	-	attention deficit hyperactive disorder
IQ	-	Intelligent Quotient
TART	-	Testicular Adrenal rest tumours.

ETHICAL COMMITTEE CLEARANCE CERTIFICATE

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.C.Rekha
Postgraduate in M.D.(Paediatrics)
Madras Medical College
Chennai – 600 003.

Dear Dr. C.Rekha,

The Institutional Ethics Committee has considered your request and approved your study titled **"Study of Physical, Social and Cognitive Functioning in Children with Congenital Adrenal Hyperplasia" No.44012015.**

The following members of Ethics Committee were present in the meeting held on 20.01.2015 conducted at Madras Medical College, Chennai-3.

1. Dr.C.Rajendran, M.D.,	: Chairperson
2. Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandini, M.D., Inst.of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC	: Member
6. Prof.Md.Ali, M.D., D.M., Prof. & HOD of Medl.G.E., MMC	: Member
7. Prof.K.Ramadevi, Director , Inst.of Biochemistry, MMC	: Member
8. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9. Prof.S.G.Sivachidambaram, M.D., Director i/c, Inst.of Internal Medicine, MMC	: Member
10. Thiru S.Rameshkumar, Administrative Officer	: Lay Person
11. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

22/1/15

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

INFORMED CONSENT FORM

(IN PATIENT'S OWN REGIONAL LANGUAGE)

Study of physical, social and cognitive functioning of children with CAH

Investigator name : Dr.Rekha.C.

Guide : Prof. Dr. S.Sundari MD ,DCH.

(To be read to caretakers in the presence of witness)

CAH is a family of autosomal recessive disorders of cortisol biosynthesis which inturn increases the production of ACTH that would cause adrenal hyperplasia and androgen excess. CAH is the most common cause of **hyperandrogenism** in children. CAH, being treated with steroids, whose growth suppresing effects combined with early epiphyseal fusion resulting from high androgens alters the growth pattern. Two types of CAH- **classic** and **non-classic**.Classic again in to two types-**simple virilising** and **salt wasting** types. Adequate androgen suppression achieved with appropriate dosage of exogenous steroids could be assessed by perfect periodic monitoring.Hyperandrogenism during early period of brain development causes social and behavioral abnormalities.Cognitive impairment occur in these patients due to iatrogenic steroids and organic changes in brain due to androgen excess in early period.

How is the study being done?

Children with congenital adrenal hyperplasia on treatment will be thoroughly evaluated by clinical history taking, clinical examination and investigations like serum electrolytes, lipid profile,blood testosterone

levels,androstenedione levels,17 hydroxy progesterone..Radiologically –x ray for bone age,USG for testicular volume. Social adaptive functioning decided from **vineland social adaptive behaviour scale.** Behavioural functioning of child screened from **child behaviour check list(CBCL).** Cognitive functioning from

1. **Gessel's child behavior schedule**
2. **Binet-Kamath Test of Intelligenc**
3. **MISIC(Malin's intelligence scale for Indian children)**

Can I refuse to join the study?

You may refuse to participate or withdraw from the study at any time. In both cases your child will be treated in the usual manner in the hospital.

Is there any benefit or harm from this study?

Your child's health status is known & also the data obtained can be used for community benefit & for the advancement of medical research. There is no harm to your child from this study.

Confidentiality:

The data collected from the study will be used for the purpose of the study only. If the results of the study are to be published personal information of the children participating in the study will be kept confidential. There will not be any disclosure about your child's information without your permission.

How will your decision to not participate in the study affect your child?

Your decisions to not to participate in this research study will not affect your child's medical care or your relationship with the investigator or the

institution. Your doctor will still take care of your child and the child will not lose any benefits to which he/she is entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during course of the study without giving any reasons.

I have been fully informed about the study and the benefits to my child and the possible harm that can happen.

This authorisation is valid only for this study. “I have understood and receive a copy of the consent form”. I agree for my child’s participation in this study.

Signature/Thumb print of the parent/guardian:

Signature of the investigator:

Witness signature:

Date:

Principal investigator:

Address:

Phone:

தகவல் படிவம்

ஆராய்ச்சி தலைப்பு

அண்ணீரகச் சுரப்பியின் பிறவி சிக்கலுக்கு சிகிச்சையிலுள்ள குழந்தைகளின் வளர்ச்சி மற்றும் அறிவாற்றல் சார்ந்த பாதிப்புகள் கண்டறியும் ஆய்வு

முதன்மை ஆய்வாளர் பெயர் : ச.ரேகா

பங்கு பெறுபவரின் பெயர் :

ஆராய்ச்சி நிலையம் : அரசு குழந்தைகள் நலமருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை-600 008.

1. ஆய்வின் நோக்கம்

அண்ணீரகச் சுரப்பியின் பிறவிச் சிக்கலால் குழந்தையின் பிறப்புறுப்பில் குறைபாடு ஏற்படலாம். அந்நோயின் சிகிச்சைக்கு கொடுக்கப்படும் மருந்தினாலும் நோயின் தன்மையாலும் ஏற்படும் வளர்ச்சி மற்றும் அறிவாற்றல் பாதிப்பும் இந்த ஆய்வின் மூலம் கண்டறியப்படும்.

2. ஆய்வின் அனுமதி

இந்த ஆய்விற்கான அனுமதி இக்கல்வி நிறுவனத்தில் ஆய்வு நெறிமுறைக் குழுவிடம் பெறப்பட்டது.

3. ஆய்வின் வடிவம்

அண்ணீரகச் சுரப்பியின் பிறவிச் சிக்கல் கண்டறியப்பட்ட குழந்தைகளுக்கு எடை, உயரம், இரத்தக் கொதிப்பு, இரத்தப் பரிசோதனை மற்றும் அறிவாற்றல் பரிசோதனை செய்யப்படும்.

4. ஆய்வு முறை

நாளமில்லா சுரப்பி பிரிவிற்கு வரும் அண்ணீரகச் சுரப்பியின் பிறவிச் சிக்கல் கண்டறியப்பட்ட குழந்தைகளிடமிருந்து பரிசோதனை விபரங்கள் சேகரிக்கப்படும்.

அக்குழந்தைகளுக்கு உடல் பரிசோதனையும், இரத்தப் பரிசோதனையும், அறிவாற்றல் பரிசோதனையும் செய்து, குறைபாடு ஏதேனும் இருந்தால் கண்டறியப்படும்.

5. **ஆய்வினால் மக்களுக்கு ஏற்படும் நன்மைகள்**

ஆய்வில் செய்யப்பட்டுள்ள பரிசோதனையில் உயரமோ அல்லது எடையோ அல்லது இரத்தப் பரிசோதனையில் ஏதேனும் குறைக்கண்டறியப்பட்டால் அதற்கு ஏற்ப மருந்தின் அளவு மாற்றப்படும்.

6. உங்கள் குழந்தையைப் பற்றிய தனிப்பட்ட விபரங்கள் யாருக்கும் தெரியாமல் பாதுகாக்கப்படும்.

7. இந்த ஆய்வில் பங்கு பெறுவது உங்கள் தனிப்பட்ட விருப்பமே. ஆய்வில் பங்கு பெறுவதில் விருப்பமில்லை என்றால் விலகிக் கொள்ளலாம். அவ்வாறு விலகுவது தங்கள் குழந்தையின் சிகிச்சைக்கு எவ்வித பாதிப்பையும் உருவாக்காது.

8. ஆய்வின் முடிவுகள் (தேவை ஏற்படின்) ஆய்வு நடக்கும்போதோ அல்லது ஆய்வு முடிந்த பின்னரோ தங்களுக்குத் தெரிவிக்கப்படும். அந்த முடிவுகள் தங்கள் குழந்தையின் சிகிச்சைக்குப் பேருதவியாக இருக்கக்கூடும்.

ஆய்வாளரின் கையொப்பம் பெற்றோர்/காப்பாளர் கையொப்பம்

நாள் :

இடம் :

ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு

அண்ணீரகச் சுரப்பியின் பிறவி சிக்கலுக்கு சிகிச்சையிலுள்ள குழந்தைகளின் வளர்ச்சி மற்றும் அறிவாற்றல் சார்ந்த பாதிப்புகள் கண்டறியும் ஆய்வு

ஆராய்ச்சி நிலையம் : அரசு குழந்தைகள் நலமருத்துவமனை மற்றும் ஆராய்ச்சி நிலையம், எழும்பூர், சென்னை-600 008.

பங்கு பெறுபவரின் பெயர் :

பாலினம் :

1) இந்த ஆய்வைப் பற்றிய அனைத்துத் தகவல்களும் எனக்கு தெரிவிக்கப்பட்டது.
2) இந்த ஆய்வில் பங்குபெறுவதற்கான ஒப்புதல் படிவம் பற்றியும் எனக்கு விவரிக்கப்பட்டது.
3) இந்த ஆராய்ச்சியின் தன்மையும், எனது உரிமைகளும் எடுத்துரைக்கப்பட்டது.
4) எனது குழந்தை எடுத்துக் கொண்ட அனைத்து நவீன அறிவியல் சார் மருத்துவம் மற்றும் இதர சிகிச்சை முறைகள் பற்றி ஆய்வாளருக்குத் தெரிவிப்பேன்.
5) இந்த ஆய்வினால் எனது குழந்தையின் நலனுக்கு எந்த தீங்கும் இல்லை என்பதைத் தெரிந்து கொண்டேன்.
6) எனது குழந்தை கடந்த காலத்தில் வேறு எந்த ஆய்விலும் பங்கு கொள்ளவில்லை.
7) எனது குழந்தை எந்த நேரத்திலும், இந்த ஆய்விலிருந்து விலகிக் கொள்ளலாம். மேலும் அவ்வாறு விலகுவது எந்த வகையிலும் எனது குழந்தையின் சிகிச்சையை இந்த மருத்துவமனையில் பாதிக்காது என்பதை அறிந்து கொண்டேன்.
8) ஆய்வாளர் எனது அனுமதியின்றி, எனது குழந்தையை எந்த நேரத்திலும் ஆய்விலிருந்து விலக்கிக் கொள்ளலாம் என்பதைத் தெரிந்து கொண்டேன்.
9) இந்த ஆய்வில் என் மூலம் தெரிந்து கொண்ட எனது குழந்தையைப் பற்றிய தகவல்களை, அரசு நிறுவனங்களுக்கோ (அ) கல்விசார் தேவைகளுக்காகவோ வெளியிட அனுமதிக்கிறேன்.
10) என்னுடைய குழந்தையைப் பற்றிய தனிப்பட்ட விவரங்கள் பாதுகாக்கப்படும் என்பதை தெரிந்து கொண்டேன்.
11) இந்த ஆய்வில் எனது குழந்தை பங்குபெற எனது மனமார்ந்த ஒப்புதலை தருகிறேன்.
12) இந்த ஒப்புதல் படிவத்தின் நகல் எனக்கு அளிக்கப்படும் என்பதை அறிந்து கொண்டேன்.

ஆய்வாளரின் கையொப்பம் பெற்றோர்/காப்பாளர் கையொப்பம்

நாள் :

இடம் :

PROFOMA:

1. Name:
2. Age:
3. Gender:
4. Endocrine department No:
5. Child psychiatry dept No:
6. Parent's name:
7. Address:
8. Phone number:
9. History : Age at diagnosis:
10. Initiated treatment at:
11. Dose of steroid for the past 6 months:
12. Duration of treatment:
13. Any other significant illness:
14. Antenatal history: Maternal drug intake- yes/no
15. Birth history
16. Neonatal history
17. Developmental delay – yes/no
18. Family : H/O consanguity

H/O congenital adrenal hyperplasia-yes/no

General examination:

Anthropometry:

- Height
- Weight
- BMI

2. Vitals-

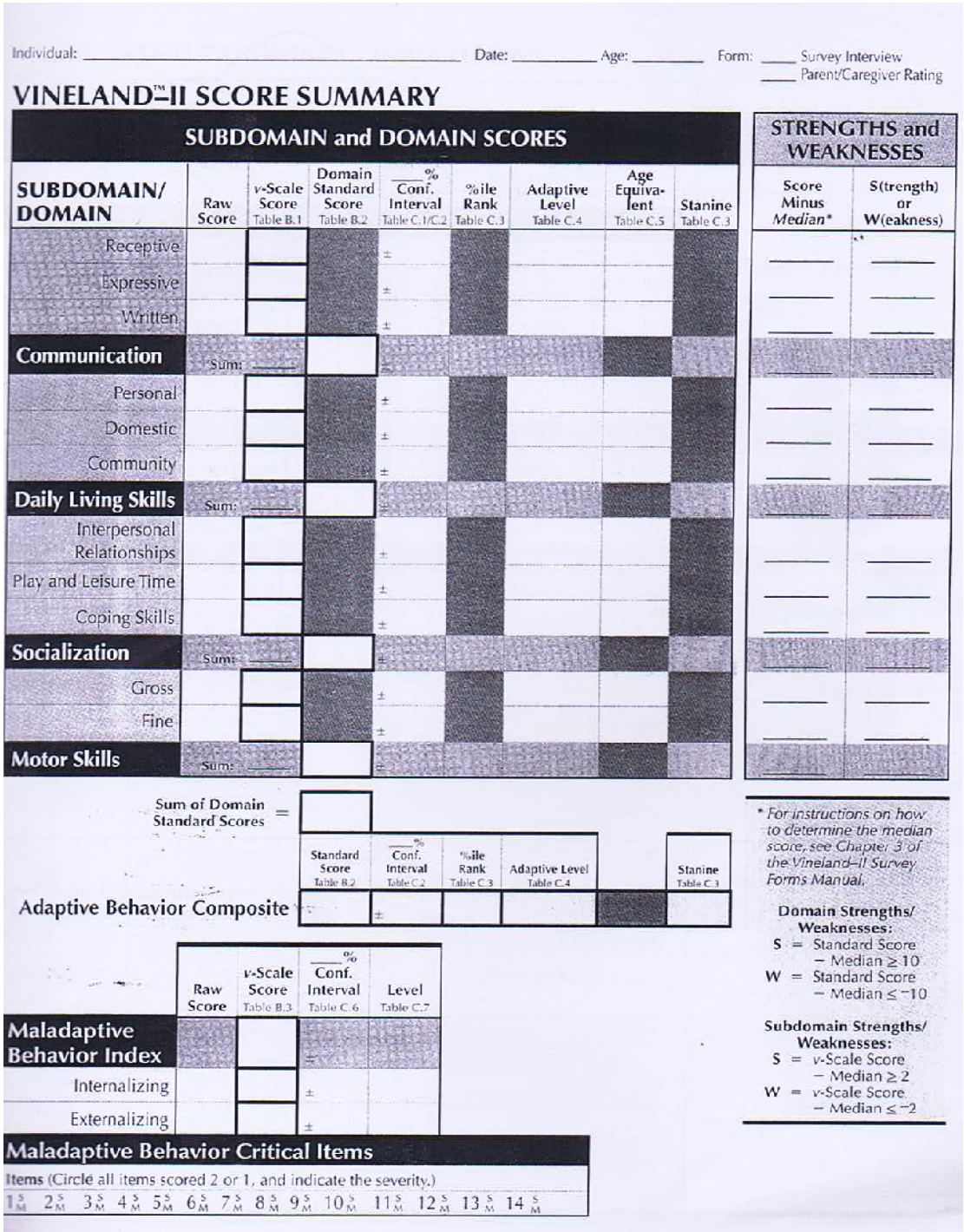
   Heart rate

   Blood pressure(plotted on standard charts)

3. Pubertal staging-tanner's staging.
4. Features of steroid excess-edema, cushingoid features, obesity, hepatomegaly.
5. Lab investigation- 17 hydroxy progesterone levels.
6. Radiologically –x ray for bone age.
7. Social adaptive functioning decided from **vineland social adaptive behavior scale.**
8. Behavioral functioning of child is screened from **child behaviour check list(CBCL) – aggression, inattention and hyperactivity.**
9. Cognitive functioning – **Gessels test**
   – **Binet-Kamath Test of Intelligence**
   – **MISIC**

VINELAND ADAPTIVE BEHAVIOUR SCALE –

SCORE SHEET



Individual: _____ Date: _____ Age: _____ Form: ____ Survey Interview ____ Parent/Caregiver Rating

VINELAND™-II SCORE SUMMARY

SUBDOMAIN and DOMAIN SCORES

SUBDOMAIN/ DOMAIN	Raw Score	v-Scale Score Table B.1	Domain Standard Score Table B.2	___% Conf. Interval Table C.1/C.2	%ile Rank Table C.3	Adaptive Level Table C.4	Age Equiva-lent Table C.5	Stanine Table C.3
Receptive				±				
Expressive				±				
Written				±				
Communication	Sum: ____			±				
Personal				±				
Domestic				±				
Community				±				
Daily Living Skills	Sum: ____			±				
Interpersonal Relationships				±				
Play and Leisure Time				±				
Coping Skills				±				
Socialization	Sum: ____			±				
Gross				±				
Fine				±				
Motor Skills	Sum: ____			±				

STRENGTHS and WEAKNESSES

Score Minus *Median**	S(trength) or W(eakness)
____	** ____
____	____
____	____
____	____
____	____
____	____
____	____
____	____
____	____
____	____
____	____

Sum of Domain Standard Scores = ____

	Standard Score Table B.2	___% Conf. Interval Table C.2	%ile Rank Table C.3	Adaptive Level Table C.4		Stanine Table C.3
Adaptive Behavior Composite		±				

	Raw Score	v-Scale Score Table B.3	___% Conf. Interval Table C.6	Level Table C.7
Maladaptive Behavior Index			±	
Internalizing			±	
Externalizing			±	

Maladaptive Behavior Critical Items

Items (Circle all items scored 2 or 1, and indicate the severity.)

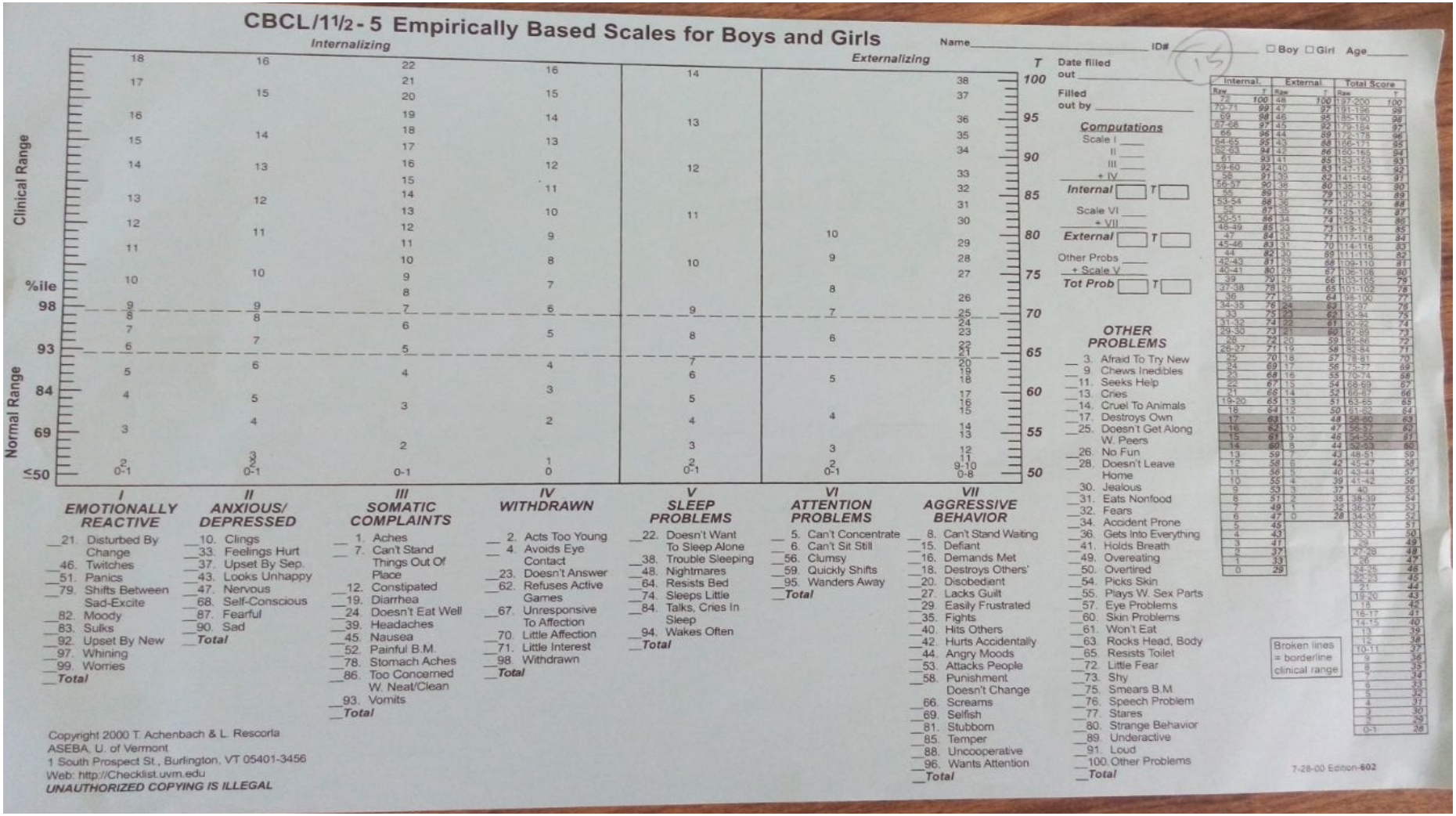
1^{S}_{M} 2^{S}_{M} 3^{S}_{M} 4^{S}_{M} 5^{S}_{M} 6^{S}_{M} 7^{S}_{M} 8^{S}_{M} 9^{S}_{M} 10^{S}_{M} 11^{S}_{M} 12^{S}_{M} 13^{S}_{M} 14^{S}_{M}

* *For instructions on how to determine the median score, see Chapter 3 of the Vineland–II Survey Forms Manual.*

Domain Strengths/ Weaknesses:
S = Standard Score − Median ≥ 10
W = Standard Score − Median ≤ −10

Subdomain Strengths/ Weaknesses:
S = v-Scale Score − Median ≥ 2
W = v-Scale Score − Median ≤ −2

CHILD BEHAVIOUR CHECK LIST



CBCL/1½-5 Empirically Based Scales for Boys and Girls

Name _____ ID# _____ ☐ Boy ☐ Girl Age _____

Internalizing | Externalizing | T

Clinical Range | Normal Range | %ile

Date filled out _____

Filled out by _____

Computations

Scale I ____
II ____
III ____
+ IV ____
Internal ☐ T ☐

Scale VI ____
+ VII ____
External ☐ T ☐

Other Probs ____
+ Scale V ____
Tot Prob ☐ T ☐

Internal		External		Total Score	
Raw	T	Raw	T	Raw	T
72	100	48	100	277-300	100
70-71	99	47	97	191-196	99
69	98	46	95	185-190	98
67-68	97	45	92	179-184	97
66	96	44	89	173-178	96
64-65	95	43	88	166-171	95
62-63	94	42	86	160-165	94
61	93	41	85	153-159	93
59-60	92	40	83	147-152	92
58	91	39	82	141-146	91
56-57	90	38	80	135-140	90
55	89	37	79	130-134	89
53-54	88	36	77	127-129	88
52	87	35	76	125-126	87
50-51	86	34	74	123-124	86
48-49	85	33	73	119-121	85
47	84	32	71	117-118	84
45-46	83	31	70	114-116	83
44	82	30	68	111-113	82
42-43	81	29	67	109-110	81
40-41	80	28	65	106-108	80
39	79	27	64	103-105	79
37-38	78	26	62	101-102	78
36	77	25	61	98-100	77
34-35	76	24	59	95-97	76
33	75	23	58	93-94	75
31-32	74	22	56	90-92	74
29-30	73	21	55	87-89	73
28	72	20	53	85-86	72
26-27	71	19	52	82-84	71
25	70	18	50	79-81	70
24	69	17	49	76-78	69
23	68	16	47	74-75	68
22	67	15	46	71-73	67
21	66	14	44	68-70	66
19-20	65	13	43	66-67	65
18	64	12	41	63-65	64
17	63	11	40	60-62	63
16	62	10	38	58-59	62
15	61	9	37	55-57	61
14	60	8	35	52-54	60
13	59	7	34	50-51	59
12	58	6	32	47-49	58
11	56	5	31	44-46	57
10	55	4	29	41-43	56
9	53	3	28	40	55
8	51	2		38-39	54
7	49	1		36-37	53
6	47	0		34-35	52
5	45			32-33	51
4	43			30-31	50
3	41			29	49
2	37			27-28	48
1	33			26	47
0	29			24-25	46
				22-23	45
				21	44
				19-20	43
				18	42
				16-17	41
				14-15	40
				13	39
				12	38
				10-11	37
				9	36
				8	35
				7	34
				6	33
				5	32
				4	31
				3	30
				2	29
				0-1	28

Broken lines = borderline clinical range

I EMOTIONALLY REACTIVE

__21. Disturbed By Change
__46. Twitches
__51. Panics
__79. Shifts Between Sad-Excite
__82. Moody
__83. Sulks
__92. Upset By New
__97. Whining
__99. Worries
__*Total*

II ANXIOUS/ DEPRESSED

__10. Clings
__33. Feelings Hurt
__37. Upset By Sep.
__43. Looks Unhappy
__47. Nervous
__68. Self-Conscious
__87. Fearful
__90. Sad
__*Total*

III SOMATIC COMPLAINTS

__ 1. Aches
__ 7. Can't Stand Things Out Of Place
__12. Constipated
__19. Diarrhea
__24. Doesn't Eat Well
__39. Headaches
__45. Nausea
__52. Painful B.M.
__78. Stomach Aches
__86. Too Concerned W. Neat/Clean
__93. Vomits
__*Total*

IV WITHDRAWN

__ 2. Acts Too Young
__ 4. Avoids Eye Contact
__23. Doesn't Answer
__62. Refuses Active Games
__67. Unresponsive To Affection
__70. Little Affection
__71. Little Interest
__98. Withdrawn
__*Total*

V SLEEP PROBLEMS

__22. Doesn't Want To Sleep Alone
__38. Trouble Sleeping
__48. Nightmares
__64. Resists Bed
__74. Sleeps Little
__84. Talks, Cries In Sleep
__94. Wakes Often
__*Total*

VI ATTENTION PROBLEMS

__ 5. Can't Concentrate
__ 6. Can't Sit Still
__56. Clumsy
__59. Quickly Shifts
__95. Wanders Away
__*Total*

VII AGGRESSIVE BEHAVIOR

__ 8. Can't Stand Waiting
__15. Defiant
__16. Demands Met
__18. Destroys Others'
__20. Disobedient
__27. Lacks Guilt
__29. Easily Frustrated
__35. Fights
__40. Hits Others
__42. Hurts Accidentally
__44. Angry Moods
__53. Attacks People
__58. Punishment Doesn't Change
__66. Screams
__69. Selfish
__81. Stubborn
__85. Temper
__88. Uncooperative
__96. Wants Attention
__*Total*

OTHER PROBLEMS

__ 3. Afraid To Try New
__ 9. Chews Inedibles
__11. Seeks Help
__13. Cries
__14. Cruel To Animals
__17. Destroys Own
__25. Doesn't Get Along W. Peers
__26. No Fun
__28. Doesn't Leave Home
__30. Jealous
__31. Eats Nonfood
__32. Fears
__34. Accident Prone
__36. Gets Into Everything
__41. Holds Breath
__49. Overeating
__50. Overtired
__54. Picks Skin
__55. Plays W. Sex Parts
__57. Eye Problems
__60. Skin Problems
__61. Won't Eat
__63. Rocks Head, Body
__65. Resists Toilet
__72. Little Fear
__73. Shy
__75. Smears B.M.
__76. Speech Problem
__77. Stares
__80. Strange Behavior
__89. Underactive
__91. Loud
__100. Other Problems
__*Total*

7-28-00 Edition-602

MALIN'S INTELLIGENCE SCALE FOR INDIAN CHILDREN

6 YEARS

CONVERSION OF RAW SCORES TO PERCENTILE I.Q.'s. or T.Q.'s

VERBAL												PERFORMANCE											
Infor.		Comp.		Arith		Simil.		Vocab.		Digit		Picture		Block		Object		Coding		Maze	
R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.
1	60	1	65	1	65	1	75	1-2	55-57	1	62	1	60	1	75	1	67	1-2	55-57	1	75
2	65	2	75	2	75	2	85	3-4	60-62	2	68	2	66	2	79	2	69	3-4	59-61	2	80
3	70	3	80	3	80	3	91	5-6	65-67	3	75	3	72	3	83	3	75	5-6	63-65	3	85
4	75	4	85	4	85	4	98	7-8	70-72	4	80	4	80	4	89	4	92	7-8	67-69	4	89
5	85	5	93	5	95	5	105	9-10	75-78	5	85	5	89	5	96	5	100	9-10	71-73	5	93
6	93	6	100	6	105	6	112	11-12	80-83	6	93	6	95	6	103	6	104	11-12	75-76	6	96
7	100	7	106	7	115	7	119	13-14	85-88	7	100	7	104	7	108	7	108	13-14	77-78	7	100
8	108	8	113	8	125	8	125	15	90	8	110	8	111	8	112	8	112	15-16	79-80	8	104
9	115	9	119	9	135	9	133	16	93	9	119	9	119	9	117	9	116	17-18	81-82	9	107
10	123	10	126	10	145	10	140	17	95	10	129	10	127	10	121	10	119	19-20	83-84	10	111
11	130	11	132	11	155	11	147	18	98	11	139	11	135	11	126	11	123	21-22	85-87	11	115
12	138	12	139	12	165	12	155	19	100	12	148	12	140	12	130	12	127	23-24	89-91	12	119
13	145	13	145				162	20	103	13	158	13	145	13	135	13	131	25-26	93-94	13	123
14	155	14	152					21	106			14	150	14	140	14	135	27-28	96-98	14	126
15	165							22	109			15	155	15	145	15	140	29-30	100-102	15	130
								23	112					16	150	16	145	31-32	103-104	16	135
								24	115					17	155	17	150	33-34	105-107	17	140
								25	118							18	155	35-36	108-109	18	145
								26-27	120-123									37-38	111-112	19	150
								28-29	125-127									39-40	114-115	20	155
								30-31	130-132									41-42	117-120		
								32-33	134-137									43-44	122-125		
								34-35	139-141									45-46	127-130		
								36-37	143-146									47-48	132-135		
								38-39	148-150									49-50	137-140		
								40-41	153-155									51-52	142-145		
																		53-54	147-150		
																		55-56	152-155		

7 YEARS

CONVERSION OF RAW SCORES TO PERCENTILE I.Q.'s. or T.Q.'s.

VERBAL												PERFORMANCE											
Infor.		Comp.		Arith		Simil.		Vocab.		Digit		Picture		Block		Object		Coding		Maze	
R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.	R.S.	T.Q.
1	59	1	62	1	62	1	65	1-2	55-57	1	60	1	60	1	65	1	59	1-6	55-60	1	65
2	63	2	68	2	68	2	75	3-4	59-61	2	65	2	65	2	75	2	63	7-11	62-66	2	75
3	67	3	75	3	75	3	85	5-6	63-64	3	70	3	70	3	80	3	67	12-15	67-70	3	78
4	71	4	80	4	81	4	93	7-8	66-68	4	75	4	75	4	85	4	71	16-17	72-73	4	81
5	75	5	85	5	87	5	100	9-10	70-72	5	80	5	85	5	93	5	75	18-19	74-75	5	84
6	85	6	90	6	100	6	105	11-12	73-75	6	85	6	90	6	100	6	92	20-21	78-80	6	87
7	91	7	96	7	110	7	111	13-14	80-82	7	91	7	95	7	104	7	100	22-23	83-85	7	91
8	98	8	101	8	120	8	117	15-16	82-85	8	97	8	100	8	108	8	104	24-25	86-88	8	95
9	104	9	106	9	129	9	123	17	87	9	103	9	106	9	113	9	112	26-28	89-91	9	100
10	111	10	111	10	139	10	128	18	90	10	110	10	112	10	117	10	118	29-32	93-96	10	103
11	118	11	116	11	149	11	134	19	93	11	117	11	118	11	121	11	124	33-36	98-101	11	106
12	123	12	121	12	159	12	140	20	95	12	125	12	124	12	126	12	130	37-40	103-107	12	109
13	129	13	125			13	146	21	98	13	132	13	130	13	130	13	136	41-42	109-111	13	112
14	135	14	130			14	152	22	100	14	139	14	136	14	135	14	142	43-45	112-114	14	115
15	140	15	135			15	158	23	103	15	147	15	143	15	139	15	148	45-46	115-117	15	122
16	145	16	140			16	165	24	106	16	155	16	149	16	143	16	155	47-48	118-120	16	128
17	152	17	145					25	109	17	162	17	155	17	148			49-50	122-124	17	135
18	158	18	150					26-27	112-115					18	153			51-52	125-127	18	141

KEY TO MASTER SHEET

1.	Gender	1 - male, 2 - female
2.	Type of disease	1 - salt wasting, 2- simple virilising
3.	Consanguity	1 – consanguineous, 2 – non-consanguineous
4.	Sibling history	1- affected, 2- not affected
5.	BMI	1 – obesity 2 – over weight, 3 – normal, 4 – underweight
6.	Blood pressure	1 - < 90^{th} percentile, 2 – 90 to 95^{th} percentile, 3 - >95^{th} percentile
7.	Features of steroid excess	0 – absent, 1 – present
8.	X-ray for bone age	-1 bone age delayed by 1 year -2 bone age delayed by 2 years 0 bone age corresponds chronological age

		1 bone age advanced by 1 year
		2 bone age advanced by 2 years
		2 bone age advanced by 3 years
9.	CBCL	0 – not aggressive,
		1 - aggressive
10.	ADHD	0 – no ADHD,
		1 – ADHD

Others:

1. Age of the child mentioned in years.
2. Age at diagnosis mentioned in months.
3. Dose of steroid in mg/m2 body surface area.
4. Duration of treatment in months.
5. Height and weight are mentioned in corresponding z-scores.
6. 17OHP in ng/ml.
7. Social adaptive behavior as composite score from vineland adaptive behavior scale.
8. IQ mentioned in percentage.

MASTER CHART

sr no	Name	gender	age	age_diag	dose_steriod	dur_treT	TYP_DISEASE	consanguity	siblings	height	weight	BMI	sys_BP	dias_BP	SMR	steroid_exce	TIQHP	x_rayBA	vineland	CBCL	IQ	ass. ADHD
1	Sathiya priya	2	9	1	15	108	1	1	1	-0.29	1.6	1	2	2	1	1	0.45	-1	83	0	87	0
2	ponnarasu	1	3	1	15	36	2	1	2	0.5	0.3	3	1	1	1	0	0.08	-1	92	0	90	0
3	navashree	2	6	1	20	72	1	1	2	-0.7	0.08	2	1	1	1	1	0.3	-1	82	1	80	1
4	nithya	2	11	18	15	114	1	1	2	4.1	3.7	4	1	1	1	0	15.2	1	74	0	71	0
5	oviyashree	2	6	1	15	72	2	1	1	0.08	0.6	2	1	1	1	0	0.29	0	86	0	81	0
6	vidyashree	2	8	36	20	60	2	1	1	-1.9	0.5	1	2	2	1	1	0.5	-1	93	0	92	0
7	srihashini	2	8	1	19	96	2	2	2	-1.6	-0.9	3	1	1	1	0	147.8	0	98	1	108	1
8	janani	2	6	1	9	72	2	1	2	-1.8	-2.4	4	1	1	2	0	86	1	78	0	76	0
9	valliyammal	2	8	1	15	96	2	1	2	0.7	0.2	3	1	1	1	0	2	0	93	0	90	0
10	dhivya	2	9	1	12	108	1	1	2	0.4	-0.6	3	1	1	1	0	3.4	0	88	0	92	0
11	ajith	1	11	1	8	132	1	1	2	4.2	3.2	4	1	1	3	0	48.6	3	75	0	74	0
12	jayasree	2	12	1	25	144	1	1	2	-2.5	2.9	1	2	2	1	1	3	-1	84	0	80	0
13	boomika	2	8	72	18	24	2	2	2	1.9	1.5	2	1	1	1	0	0.26	0	96	0	97	0
14	barkath nisha	2	6	1	22	72	1	1	2	-2	-0.9	3	1	1	1	0	0.11	-1	74	0	78	0
15	yuvarani	2	12	1	20	144	1	1	2	-1.17	1.04	1	2	1	1	1	0.24	0	93	1	90	1
16	harini	2	2	1	18	24	2	2	2	-0.7	-3.5	3	1	1	1	0	41.8	0	96	0	90	0
17	ramya	2	7	1	16	84	1	1	2	2.7	0.8	2	1	1	1	0	0.18	0	90	0	93	0
18	nithishkumar	1	11	1	12	132	1	1	2	-1.05	0.5	2	1	1	1	0	8.9	-1	85	0	86	0
19	supriya	2	12	1	16	144	1	1	2	-2.8	-0.09	2	2	2	1	1	0.22	-1	86	0	89	0
20	balaji	1	10	1	14	120	2	1	1	-0.9	-0.008	3	1	1	1	1	3.64	0	84	0	84	0
21	derik	1	8	12	19	84	2	2	2	-3.05	0.03	1	2	2	1	1	0.12	-1	70	0	64	0
22	balaji	1	9	3	14	105	2	1	1	-3.08	-1.19	3	1	1	2	0	0.07	0	72	0	70	0
23	mercelin amli	2	9	1	18	108	1	1	1	1.55	0.74	3	1	1	1	0	1.51	0	96	1	99	1
24	jervin	1	7	1	20	84	2	1	1	3.07	1.4	3	1	1	1	0	3.45	0	95	1	94	1
25	kanmanipriya	2	2	1	15	24	1	1	2	-0.12	-1.132	3	1	1	1	0	0.31	0	82	0	80	0
26	kowshika	2	6	1	13	72	2	1	2	-1.32	-2.4	4	1	1	1	0	0.66	0	86	1	82	0
27	jeevadharshini	2	6	1	24	72	1	1	2	-3.02	-1.8	3	1	1	1	0	1.2	-1	72	0	71	0

sr no	Name	gender	age	age_diag	dose_steriod	dur_treT	TYP_DISEASE	consanguity	siblings	height	weight	BMI	sys_BP	dias_BP	SMR	steroid_excess	17OHP	x_rayBA	vineland	CBCL	IQ	ass. ADHD
28	stella	2	4	1	6.5	48	1	1	2	4.4	-2.2	4	1	1	2	0	8.04	2	95	0	94	0
29	sandhiya	2	12	1	13	144	2	1	1	-3.3	-0.21	3	1	1	1	0	8.78	0	74	0	73	0
30	sheeba	2	6	1	12	72	2	1	1	0.08	0.35	3	1	1	1	0	0.11	0	76	0	74	0
31	supriya	2	4	1	28	48	1	1	2	-3.8	1.8	1	2	1	1	1	0.28	-2	64	0	68	0
32	banupriya	2	11	1	10	132	1	1	2	-0.74	-0.7	3	1	1	2	0	4.2	2	76	0	78	0
33	shakthi	2	3	1	12	36	1	1	2	-1.32	-1.13	3	1	1	1	0	41.8	0	98	0	98	1
34	abi	2	6	1	13	72	1	2	2	0.08	0.08	3	1	1	1	0	3	0	94	0	90	0
35	asma	2	7	1	15	84	1	2	2	-1.56	-2.05	3	1	1	1	0	0.8	0	73	0	74	0
36	bavana	2	2	1	14	36	2	1	2	-0.7	-1.13	3	1	1	1	0	1.4	0	82	0	80	0
37	thilagavathi	2	11	18	23	114	2	1	2	0.24	2.08	1	2	2	1	1	2.14	-2	76	0	78	0
38	mariya roselin	2	12	1	20	144	2	1	2	3.2	0.02	3	1	1	2	0	7.45	2	96	1	98	0
39	kanaga	2	2	1	15	24	1	1	2	-0.03	1.83	1	1	1	1	1	0.4	-1	86	0	84	0
40	durga	2	11	1	15	132	1	1	2	0.4	0.32	3	1	1	1	0	0.12	-1	92	0	90	0
41	priya	2	12	1	20	144	1	1	2	-0.072	0.09	2	2	2	1	1	0.31	-1	82	1	86	0
42	kumar	1	10	1	15	120	1	1	2	4.3	3.7	4	1	1	1	0	15.1	1	70	0	70	0
43	sephina	2	4	1	15	48	1	2	2	0.08	0.63	2	2	1	1	0	0.3	0	82	0	80	0
44	rajesh	1	3	14	20	22	2	1	2	-1.8	0.51	1	2	2	1	1	0.48	-1	92	1	90	0
45	ilakiya	2	3	1	19	36	1	1	2	-1.63	-0.92	3	1	1	1	0	86.1	0	102	0	104	1
46	dhivya	2	4	1	10	48	1	1	2	-1.79	-0.43	4	1	1	2	0	72	1	78	0	72	1
47	udaya	2	5	1	14	60	1	1	2	0.74	0.21	3	1	1	1	0	2	0	92	0	90	0
48	ezilarasi	2	3	1	13	36	1	2	2	0.41	-0.63	3	1	1	1	0	3.4	0	94	0	92	0
49	thanshika	2	6	1	10	72	1	1	2	3.9	3.2	4	1	1	3	0	44	3	68	0	76	0
50	kanimozhi	2	2	1	22	24	1	1	2	-2.5	2.91	1	2	2	1	1	3	-1	86	1	80	0
51	ramya	2	6	24	20	48	2	1	2	1.9	1.53	2	1	1	1	0	0.24	0	94	0	96	0
52	alfia	2	3	1	18	36	1	1	2	-2.1	-0.9	3	1	1	1	0	0.18	-1	74	0	78	0
53	anuchitra	2	6	1	20	72	1	1	2	-1.16	1.03	1	1	1	1	1	0.23	0	92	1	90	0
54	rakesh	1	7	24	18	60	2	1	2	-0.69	-3.48	3	1	1	1	0	38	0	95	0	90	0
55	maheshwari	2	4	1	16	48	1	1	2	2.69	0.78	2	1	1	1	0	0.16	0	92	0	93	0